RENEWAL-AF: A NOVEL QUANTITATIVE METHOD ASSESSING FIBRILLATORY DYNAMICS IN PATIENTS WITH ATRIAL FIBRILLATION. MECHANISTIC AND THERAPEUTIC IMPLICATIONS

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List of Abbreviations

Abbreviation	Definition
AF	Atrial fibrillation
APD	Action Potential duration
BMI	Body mass index
BB	Bachmann's bundle
CMR	Cardiac Magnetic Resonance Imaging
CT	Crista terminalis
CTI	Cavo tricuspid isthmus
CFAE	Complex Fractionated Electrograms

CPAP	Continuous positive airway pressure
DCCV	Direct current cardioversion
DF	Dominant Frequency
EED	Endocardial epicardial dissociation
ERP	Effective Refractory Period
FACM	Fibrotic atrial cardiomyopathy
GJ	Gap junction
GLS	Global longitudinal strain
ICC	Intraclass coefficient
IAS	Interatrium septum
IQR	Interquartile range
LA	Left atrium
LV	Left ventricle
LVA	Low voltage area
LAVi	Left atrium volume index
LSPV	Left superior pulmonary vein
LIPV	Left inferior pulmonary vein
LGE	Late gadolinium enhancement
LAA	Left atrial appendage
LVEF	Left ventricular ejection fraction
λ_f	Rate of phase singularity formation
λ_d	Rate of phase singularity destruction
MACE	Major adverse cardiovascular events
MMP	Matrix metalloproteinases
OSA	Obstructive sleep apnea
PAF	Paroxysmal atrial fibrillation
PersAF	Persistent atrial fibrillation
PV	Pulmonary veins
PVI	Pulmonary vein isolation
PM	Pectinate muscle
PH	Pulmonary hypertension
PS	Phase singularities
RA	Right atrium
RAA	Right atrium appendage
RSPV	Right superior pulmonary vein
RIPV	Right inferior pulmonary vein
Rho (λ_f / λ_d)	Ratio of rate of phase singularity formation versus destruction
SVC	Superior vena cava
SHeN	Shannon entropy

SD	Standard deviation
VF	Ventricular fibrillation

Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice and is associated with significant comorbidities including increased risk of stroke, dementia, and death. Drug therapies for AF are partially efficacious with significant side effects while success rates from catheter ablation procedure remain suboptimal, despite improvement in catheter ablation and mapping techniques. Currently observed limitations of clinical success from antiarrhythmics/therapeutic procedures may be a consequence of a key pertinent issues, including: 1) opposing ideas behind mechanisms driving persistent AF (rotors versus multiple wavelets) are incompletely clearly defined; 2) temporally-based clinical classification of patients with AF may not reflect a patient's true AF pathobiology, with an improved classification of AF involving assessment of underlying structural or electrical remodeling associated with AF progression being needed to individualise therapeutic strategies for AF patients ; and 3) the relative paucity robust validated quantitative assessment tools to understand fibrillatory dynamics. Currently, available mapping techniques rely heavily on qualitative assessment and observation, which by itself, has significant limitations including electrode density, poor contact with the endocardial surface, and false positive/negative detection of rotors.

The presence of rotors in AF, both paroxysmal and persistent forms have been observed for decades. Rotors are functional re-entries, with an excitable but unexcited core. More recently, there have been several efforts developing focused approaches to target rotors in AF as they are thought to be "drivers" in persistent AF. However, clinical outcomes from this approach have been mixed. Considering these variable outcomes, we have recently shown in animal models, optical mapping data and computer simulations that the lifetime and inter-arrival times for these rotors follow an exponential curve,

consistent with the notion that rotors may be able to be modelled as occurring via Poisson processes. A systematic review performed showed similar exponential curves of the rotor lifetime and inter-formation times from six previously published studies. From a mechanistic perspective, by demonstrating rotor formation and destruction events follow a Poisson process, this has recast the mechanism of fibrillation from that of one or two dominant rotors driving fibrillation to that of a continuous, independent regeneration and degeneration of rotors in the atrium. From a therapeutic perspective, this provides us with a potentially measurable metric, referred to as λ_f/λ_d, which is given by the ratio of λ_f (rate of rotor formation) and λ_d (rate of rotor destruction). λ_f/λ_d has been shown to be individualised for different AF patients, which means it could potentially be used as a target for modulation in a drug-based intervention or catheter ablation strategy. The main purpose of this study is to therefore determine the relevance of λ_f/λ_d to known clinical, structural, and electrical correlates associated with AF progression. Additionally, we will further observe the effect of catheter ablation therapy and antiarrhythmic drug therapy during catheter ablation procedures on the metric λ_f/λ_d.

In chapter 2, we seek to understand the variation and spatiotemporal distribution of λ_f/λ_d through sampling in sixteen different locations in the atrium. The reason for this is that in AF, pulmonary vein isolation (PVI) remains the cornerstone for AF ablation, while additional ablation strategies (posterior wall isolation, roof line, superior vena cava isolation, mitral isthmus line, isolation of the left atrial appendage, targeting complex fractionated area or targeting rotors) remains at the discretion of the treating physician. By delineating the regional differences in λ_f/λ_d, it could help physicians individualise their ablation strategy, hypothetically according to zones with higher rates of λ_f/λ_d.

In chapter 3, we seek to understand the correlation between the rate of rotor formation λ_f and the rate of rotor destruction λ_d between left and right atria in atrial regions connected anatomically and electrically by interatrial pathways. Mechanistically, these interatrial pathways have been thought to contribute to the maintenance of AF. However, studies looking at the contributions of these respective interatrial

pathways for fibrillatory propagation during AF have been lacking. Clinically, while some observational studies do suggest there may be a clinical benefit of ablations targeting these interatrial pathways, no large, randomised studies have been conducted to date, partly due to difficulty defining AF patients who would benefit from these additional ablation strategies.

In Chapter 4, we seek to develop a new classification of AF by establishing AF Phenogroups using the renewal theory approach and seek to understand the correlation between λ_f and λ_d with patients' baseline clinical characteristics and clinical outcomes at 6 and 12 months. Clinical outcomes measured include the need for re-do AF ablation procedure, AF-related hospitalisations, the need for DCCV, and the need for intensification of AF therapy (increase in the dose of antiarrhythmic therapy or change to any antiarrhythmic therapy to amiodarone). The need for any type of antiarrhythmic therapy to maintain sinus rhythm will be documented. AF burden will be measured using an external Alivecor cardiac monitor for six months.

In Chapter 5, we aim to investigate the correlations between renewal theory-based fibrillatory dynamic analysis and markers of structural and functional remodeling in the left atrium, using the renewal theory approach. Structural and functional remodeling of the atria underlies AF progression, from shorter paroxysms to longer, persisting episodes. We hypothesise that AF Phenogroup, derived from the renewal theory approach, will significantly correlate with echocardiographic markers of left atrial structural and functional remodeling.

In Chapter 6, we aim to explore the mechanistic role of the right atrium in AF maintenance using renewal theory-based fibrillatory dynamic analysis. Some studies have suggested potential clinical benefits from targeted RA ablation in AF, but these results were not consistently reproducible in other studies. The inconsistent clinical benefit observed likely stems from our lack of understanding of the role of RA in AF and how this defers between individuals. It is plausible that a subset of AF patients who could benefit

from targeted RA ablation exists and characterization of this group of patients will be key to improving clinical benefits from RA ablation.

The presence of AF in patients with heart failure has been associated with adverse clinical outcomes. In Chapter 7, we aim to investigate the effects of subclinical LV systolic dysfunction, measured echocardiographically using LV global longitudinal strain (LV GLS) on LA structural and functional parameters and the spatial distribution of renewal rate constants in the LA. We hypothesise that subclinical LV systolic dysfunction will be associated with adverse LA structural and functional parameters. Additionally, we also hypothesise that a characteristic distribution of rate constants in the LA will be observed in patients with heart failure, compared to controls (patients with normal LV GLS).

In Chapter 8, we aim to investigate the relationship between renewal rate constants with dominant frequency measurement, a quantitative measure of the rate of activation of the atria. It has been hypothesised that atrial regions with the highest dominant frequency represent “drivers” in selected AF patients. However, clinical studies with ablation targeting atrial regions with the highest dominant frequency have not consistently shown improved clinical outcomes post-ablation. Furthermore, it has been recognised that there are physiologic limitations to the use of dominant frequency in the quantification of AF fibrillatory dynamics. We hypothesise that, given the intrinsic differences between the measurement of renewal rate constants and dominant frequency, there will be no correlation between these two measures.

In Chapter 9, we provide a concise summary of all the pertinent findings from earlier chapters and how these findings add to the current knowledge and potential directions for future studies.

DECLARATION

I certify that this thesis:

1. does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university

2. and the research within will not be submitted for any other future degree or diploma without the permission of Flinders University; and

3. to the best of my knowledge and belief, does not contain any material previously published or written by another person except where due reference is made in the text; and

4. has been completed without the use of generative artificial intelligence tools.

Jing Xian Quah

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Peer-Reviewed Publications

Chapter 1

Quah, J, Dharmaprani, D, Lahiri, A, et al. Prospective cross-sectional study using Poisson renewal theory to study phase singularity formation and destruction rates in atrial fibrillation (RENEWAL-AF): Study design. *J Arrhythmia*. 2020; 36: 660– 667.

Quah, JX, Dharmaprani, D, Tiver, K, et al. Atrial fibrosis and substrate-based characterisation in atrial fibrillation: Time to move forwards. *J Cardiovasc Electrophysiol*. 2021; 1- 14.

Quah JX, Dharmaprani D, Lahiri A, Tiver K, Ganesan AN. Reconceptualising Atrial Fibrillation Using Renewal Theory: A Novel Approach to the Assessment of Atrial Fibrillation Dynamics. Arrhythmia Electrophysiol Rev. 2021 Jul;10(2):77-84

Chapter 2

Quah JX, Jenkins E, Dharmaprani D, Tiver K, Smith C, Hecker T, Joseph MX, Selvanayagam JB, Tung M, Stanton T, Ahmad W, Stoyanov N, Lahiri A, Chahadi F, Singleton C, Ganesan A. Role of interatrial conduction in atrial fibrillation: Mechanistic insights from renewal theory-based fibrillatory dynamic analysis. Heart Rhythm O2. 2022 May 16;3(4):335-343.

Poster presentation Heart Rhythm Society 2022: PO-641-06 Role of interatrial conduction in atrial fibrillation. Mechanistic insights from renewal theory-based fibrillatory dynamic analysis. Alvin Quah, B Med Sc, MBBS, FRACP. DOI: https://doi.org/10.1016/j.hrthm.2022.03.150

Chapter 3

Oral presentation Heart Rhythm Society 2022: CA-529-01 Renewal theory: A statistical approach to improve patient selection for pulmonary vein isolation-only strategy in atrial fibrillation ablation. DOI: https://doi.org/10.1016/j.hrthm.2022.03.120

Chapter 1
Literature Review

1.1 Introduction

Atrial fibrillation (AF) is the most encountered cardiac rhythm disorder. It is estimated that up to one in four members of the community will develop AF at the age of 40 years and older, with a one in six risk of AF even in the absence of known AF-related risk factors such as ischemic heart disease or heart failure (1). In addition, there has been an increase in the prevalence of AF over the past decade (2, 3). This has been attributed to advancing age and the increased burden of cardiovascular risk factors (4). This is a cause for concern, as AF not only negatively impacts a patient's quality of life through symptoms such as palpitations and breathlessness, but also leads to poor clinical outcomes including a higher risk of dementia, stroke, major bleeding, heart failure and death (5-7)

From a therapeutic standpoint, the choice of rate versus rhythm control is up to the discretion of the treating physician. Although earlier studies have shown no significant difference in clinical outcomes comparing these two therapeutic methods (8, 9), there is increasing evidence of positive clinical benefits in achieving rhythm control in AF patients with heart failure (10). In addition, more recent evidence points towards the benefit of utilising an early rhythm control strategy with catheter ablation compared to antiarrhythmic therapy in patients with paroxysmal AF (PAF) (11, 12). This is not surprising as drug therapy has previously been associated with a high failure rate with a significant side effect profile (13). In patients undergoing catheter ablation, pulmonary vein isolation (PVI) remains the strategy of choice for AF ablation. Clinical efficacy of PVI in patients with paroxysmal AF, where pulmonary vein triggers are thought

to be initiating impetus for AF has previously been demonstrated. However, in patients with non-paroxysmal forms of AF, clinical success rates of PVI remain suboptimal, as in these patients AF is sustained by not only pulmonary vein triggers but also changes in the underlying atrial substrate as a consequence of progressive structural, electrical and functional remodelling (14). To illustrate, a meta-analysis performed showed that single-procedure freedom from AF after catheter ablation was only 55% in patients with paroxysmal AF and 41% in patients with persistent AF (15).

Ultimately, understanding the mechanism of AF is essential for the development of an effective ablation strategy. Multiple competing theories exist in this regard, the most prominent of these including the presence of multiple unstable wavelets and the presence of stable driving functional re-entrant electrical circuits (rotors) sustaining AF. However, ablation strategies targeting rotors or the creation of functional boundaries for the termination of electrical wavelets have so far yielded inconclusive clinical results. From a mechanistic standpoint, we have recently demonstrated in animal models, simulation models and a small group of patients with persistent AF that these chaotic, unstable re-entrant circuits are formed and destroyed at a constant long-term average rate, a finding based on a branch of mathematics known as renewal theory (16). RENEWAL-AF works to extend these findings by correlating the rates of rotor formation and destruction with patient clinical characteristics with known markers of structural and electrical left atrial (LA) remodelling associated with AF and with patients' clinical outcomes post-AF ablation. In addition, we further examine the implications of spatial variation of these rate constants within the right atrium (RA) and LA and the impact of antiarrhythmic drug therapy on these rate constants.

1.1.1 Epidemiology of atrial fibrillation and its associated economic burden

In 2010, the global prevalence of AF was estimated to be around 33.5 million people, with approximately 5 million cases diagnosed annually (17). A significant rise in the prevalence of AF has been documented over the past two decades. An epidemiologic study using the Global Health Data Exchange database

published recently found that the estimated the incidence rate of AF in 2017 was approximately 31% higher than in 1997. Future projections also concerningly, points towards an increase of >60% by 2050 (18). Estimates of AF prevalence in developed countries like Australia range between 2% to 4%, with its prevalence estimated to double over the next two decades because of an increase in aging of the population (19, 20).

Increasing AF prevalence in the community has imposed a significant burden on healthcare resources, driven by an increased number of hospitalisations (21). To illustrate, a sub-analysis of the ROCKET-AF trial has shown that up to 30% of AF patients require hospital admissions each year for both cardiovascular and non-cardiovascular causes (22). In Australia, AF-related hospitalisations were the leading cause of cardiovascular hospitalisation, the incidence of which has been increasing by 6% per year over the last 15 years (23).

Despite being a common disease, significant limitations of knowledge exist within the field of AF as will be discussed further below. To summarize:

1) Limited therapeutic options exist for AF patients.
    a. No new antiarrhythmic drug therapies have been recommended by the guidelines over the past decade, while significant cardiovascular and non-cardiovascular side effects exist with the current drug options, despite their limited clinical efficacy.
    b. A plateau of ideas regarding the choice of catheter ablation strategy for AF patients, particularly those with persistent forms beyond that of pulmonary vein isolation (24).
2) Mechanisms maintaining AF remain unclear. Two dominant but conflicting hypothesis of multiple randomly propagating wavelets versus a single stable driver sustaining AF remains central to the current understanding of the persistence of AF.

3) Temporal classification of AF into paroxysmal and persistent forms, based on the duration of AF is based on limited scientific evidence rather than via direct correlation with the underlying AF pathobiology.
4) Given the limitation of the temporal classification of AF, there has been a push towards phenotyping AF through underlying substrate changes that occur during the progression of AF. Structural atrial remodelling through atria enlargement, fibrosis and decline in atrial function can be detected through non-invasive methods (echocardiogram and delayed gadolinium enhancement on cardiac magnetic resonance imaging) and invasive methods (low voltage zones on electro-anatomical mapping). However, given the infancy of these methods in the detection of atrial fibrosis, significant limitations exist.
5) Finally, the role of different anatomical areas of the left atrium in AF persistence remains uncertain.

1.2 Atrial fibrillation. A common disease with limited therapeutic options

Current therapeutic options for AF patients include the use of antiarrhythmic drug therapy and catheter ablation. Currently, available antiarrhythmic drugs act mainly either on the cardiac sodium or potassium channels. Cardiac sodium channel blockers decrease the excitability of myocardial cells while cardiac potassium channel blockers prolong myocardial cells' action potential duration and refractory periods (13). Commonly used antiarrhythmic drugs in Australia include flecainide, sotalol and amiodarone. Despite the availability of few antiarrhythmic drug options for AF patients, the clinical efficacy of these drugs in suppressing AF remains modest and their use is also associated with both cardiac and non-cardiac side effects. For example, amiodarone, which acts on multiple cardiac ion channels, has the highest clinical efficacy for AF suppression ranging from 50-70% at 7-33 months follow-up, and is associated with side effects including pneumonitis, hepatitis, thyroid dysfunction, photosensitivity, ataxia, tremor and skin discoloration (13, 25, 26). Flecainide, on the other hand, is a selective cardiac sodium channel blocker that

has also shown moderate clinical efficacy in the suppression of AF (27). Flec SL, the largest randomised clinical trial comparing short-term (four weeks) vs long-term flecainide (six months) treatment in AF patients post electrical cardioversion showed a clinical efficacy of 60% vs 70% respectively for arrhythmia-free survival, favouring the use of long-term flecainide therapy (28). However, the use of flecainide In AF patients is contraindicated in patients with known structural heart disease or coronary artery disease (27). Other potential non-cardiovascular side effects of flecainide include dizziness, headaches and visual blurring (13). Sotalol is both a beta-blocker and cardiac potassium channel blocker that is associated with fewer non-cardiovascular side effects compared to flecainide and amiodarone (13). However, the clinical efficacy of sotalol in maintaining sinus rhythm in AF patients is also modest and ranges between 25-40% (25, 26).

In the catheter ablation realm, pulmonary vein isolation, first introduced two decades ago remains the mainstay of therapy for AF patients (29). The basis of this ablation strategy, from the initial landmark study, is that atrial ectopic beats were identified in these patients were observed to initiate AF after a burst of atrial electrical depolarization. Via suppression of these pulmonary vein atrial ectopy, AF can be prevented (29). However, clinical success rates for catheter ablation remain sub-optimal. A meta-analysis published in 2013 showed a 54.1% success rate for arrhythmia-free survival in patients with paroxysmal AF and as low as 41.8% in patients with non-paroxysmal AF after follow-up of ≥3 years after AF ablation (15). The reason behind this is most likely secondary to progressive electrical, structural and functional remodelling as a consequence of the arrhythmia itself or progression of underlying cardiac structural disease or a combination of both (30). Consequently, the underlying physiology initiating and maintaining AF shifts from a focal trigger or driver to a more substrate-based driven AF promoting anatomical and functional re-entry with the appearance of extra-pulmonary vein triggers (31, 32). With this regard, different groups have proposed different ablation strategies beyond that of PVI to increase the clinical efficacy of catheter ablation for AF. Narayan et al proposed and showed that catheter ablation for AF

patients targeting focal electrical impulses also known as “rotors” in the LA resulted in improved clinical outcome for AF patients (33). However, improved clinical efficacy from ablation of rotors (either in conjunction with PVI or without PVI) have not been observed in other observational or randomised studies (34-37). In addition, similar disappointing clinical results were also seen with other ablation strategies beyond PVI, including substrate modification ablation techniques targeting complex fractionated atrial electrograms and ablation of low-voltage areas representing areas of LA fibrosis (38, 39).

It has also been increasingly recognized that lifestyle management, particularly weight loss and modification of clinical risk factors is equally as important to reduce the burden of AF. The LEGACY trial showed that AF patients who underwent goal-directed weight loss and intensive risk factor management had a six-fold increase in freedom from AF, comparing those who have lost >10% of their weight versus those with <3% weight loss (40). Swedish Obese Subjects showed in a prospective matched cohort study that the risk of new-onset AF was 29% lower in patients who have undergone bariatric surgery compared to matched controls after a median follow-up of 19 years (41). In addition, regular aerobic exercise with improvement in exercise capacity of ≥2 METs has also been shown to reduce AF burden and improve AF-related symptoms in overweight non-permanent AF patients (42). Other forms of exercise including yoga have also been shown to improve AF burden and symptoms (43). In addition, the presence of underlying obstructive sleep apnea (OSA) has also been shown to be strongly linked to the presence of AF (44-46). This has been attributed to the increasing left atrial remodelling in patients with OSA in a dose-dependent effect (47) while treatment of OSA with continuous airway pressure (CPAP) therapy has been shown to reverse atrial remodelling (48) and also reduce the recurrence of AF in patients with OSA (49, 50). Although multiple studies have shown the feasibility of having an outpatient lifestyle clinic approach promoting positive lifestyle changes in patients (51-53), the compliance rate is often suboptimal (51), due to multiple personal barriers to participation including distance, time and transport to clinic (52). In addition, findings from a recently published meta-analysis have also suggested that weight loss does not

necessarily reduce the incidence of new AF but a weight gain of 5% does increase the risk of new-onset AF by 13% (54).

1.2.1 Limitations exist with the current classification of atrial fibrillation

The current classification of AF according to the ACC/AHA/HRS and ESC are as listed in Table 1. Temporal-based classification of AF has been used since the early 1920s, in which Lewis et al described AF as "to exist in two forms, in short paroxysms, lasting a few hours or a few days and another form which persists until death". In 1998, Gallagher et al proposed 3 clinical categories of AF (paroxysmal, persistent and permanent AF) which remains the cornerstone for classification 20 years later (55). Clinical classification of AF is used by treating physicians to individualise the choice of rate versus rhythm therapy and to dictate whether an interventional therapy would be appropriate for their patients. However, despite its convenience, the use of temporal-based classification of AF has significant limitations, as listed below, and may not correlate with the underlying pathobiology of AF.

1) There is no specific biological evidence to support the 7-day cutoff, initially proposed by Gallagher et al used to differentiate paroxysmal from persistent AF, as a marker of AF persistence (55).

2) There is a lack of correlation between the temporal persistence of AF and the clinical classification of AF. In n=1195 patients with implantable cardiac devices, 34.5% of patients with paroxysmal AF and 21.2% of patients with persistent AF showed no recordings of AF over a follow-up period of mean 349 ± 40 days (56).

3) AF burden varies over time, hence classifying AF at a single time point does not accurately reflect a patient's true underlying AF persistence. To illustrate, Kaplan et al in 2017 divided n=394 patients with an implantable cardiac device, mean age of 70.2 ± 10.9 years into three groups of AF burden; 1: no AF (no day with ≥5 min of AF) 2: low AF (<5.5 h on any given day), or 3: high AF burden (≥5.5 h in a day). After 2 years, 40% of patients with initially with no or low AF experienced

periods with high AF, whereas 59% of patients initially with high AF experienced ≥6 consecutive months with no or low AF (57).

Table 1.1: Current AF classification by ACC/AHA/HRS and ESC

Category	ACC/AHA/HRS 2014 (58)	ESC 2016 (59)
First onset	N.A.	"AF that has not been diagnosed, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms."
Paroxysmal AF	"AF that terminates spontaneously or with intervention within 7 days of onset. Episodes may recur with variable frequency."	"Self-terminating, in most cases within 48 hours. Some AF paroxysms may continue for up to 7 days. AF episodes that are cardioverted within 7 days should be considered paroxysmal."

Persistent AF	"Continuous AF that is sustained>7 days."	"AF that lasts longer than 7 days, including episodes that are terminated by cardioversion, either by cardioversion or by direct current cardioversion, after 7 days or more."
Long-standing persistent AF	"Continuous AF >12 months in duration."	"Continuous AF lasting for ≥ 1 year when it is decided to adopt a rhythm control strategy."
Permanent AF	"The term "permanent" AF is used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm. Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiological attribute of AF. Acceptance of AF may change as symptoms; efficacy of	"AF that is accepted by the patient (and physician). Hence, rhythm control interventions are, by definition, not pursued in patients with permanent AF. Should a rhythm control strategy be adopted, the arrhythmia would be re-classified as long-standing persistent AF."

	therapeutic interventions and patient and clinician preferences evolve.”	

1.3 Mechanisms of AF: Unclear despite a century of research

The two most prominent, but conflicting hypotheses regarding mechanisms sustaining AF exist: 1) the presence of multiple wavelets driving AF and 2) the presence of a stable rotor or driver sustaining AF.

Figure 1.1: Mechanisms of AF Persistence

Left: Presence of multiple wavelets driving AF. Right: Presence of mother rotor driving AF. Adapted from Nattel et al (60). Used with permission from Springer Nature.

1.3.1 Multiple wavelet hypothesis

Multiple wavelet hypothesis has underlain the understanding of mechanistic models of AF for decades. The multiple wavelet hypothesis suggests the presence of multiple randomly propagating wavelets along varying paths sustaining AF. These wavelets randomly and continuously regenerate and collide leading rise to either mutual annihilation or coalescence of wavelets generating new wavelets. This hypothesis

also suggests that changes in the underlying atrial substrate favor the formation and persistence of AF including 1) increased atrial surface area 2) alterations in the refractory period and conduction velocity between myocardial cells and 3) heterogeneity in the underlying refractory periods and conduction velocities. This was initially proposed by Moe et in the 1960S, during observations of induced AF in canine vagal nerve stimulation models (61, 62). Further computational studies by Moe suggest a critical number of 23-40 randomly propagating wavelets is needed to sustain AF (63). However, mapping studies of induced AF in canine models by Allesie et al in the 1980s suggest a lower number of wavelets, 4-6 was enough to drive AF (64). The multiple wavelet hypothesis formed the basis of the surgical Maze procedure, Atrial incisions created in the Maze procedure form anatomical barriers, redirecting electrical impulses to the ventricle, and reducing the critical mass of atria which is depolarized at the same time. The end goal of the surgical Maze was to reduce the number of wavelets present which is critical for the sustenance of AF (65, 66). More recently, replicating the canine vagal nerve stimulation AF study by Moe by using biatrial high-density mapping, Seungyup et al recently showed multiple independent focal sources (minimum of three observed) activating the atrium, with no evidence of multiple wandering wavelets or rotors seen in that study (67). However, although this study raises doubt on the original observation by Moe, as this study involves acute vagally induced AF, it does not disprove that multiple wavelets could still be a potential cause for the persistence of AF.

1.3.2 Mother rotor hypothesis

In the 1990s, the concept of rotors sustaining AF was introduced. This was based on the observation of optical mapping data showing that the presence of one or two drivers was critical and important in sustaining AF (68). This brought rise to the concept of “mother rotors” sustaining AF in the early 2000s (69). In this paper, Jalife described rotors as the “primary engine of cardiac fibrillation” driven by an underlying spatiotemporal organization of electrical waves with varying behaviours including; 1) meandering rotors leading to complex electrical activation patterns and 2) high-frequency activation of

the atria secondary to uninterrupted electrical activity from stationary rotors (69). While many studies have potentially shown the presence of localized repetitive activation sources in atria driving AF (70-73), similar observations were not seen in other studies (74, 75). Importantly, targeting these "drivers" of AF which theoretically should improve clinical outcomes for AF ablation, clinical success to date has so far been disappointing in observational and randomised studies (34, 35, 76).

The lack of clinical success from targeted rotor ablation in AF may stem from a few issues:

1) When is a rotor considered to be a driver for AF or what is the definition of a clinically significant rotor? In the study by Tilz, two FIRM maps were created, and rotors identified by at least two consecutive maps were targeted for ablation (77). In the study by Balouch, rotors in a "spatially contiguous area" present in two of the three maps were targeted (78) whereas in another study, rotors present consistently in spatial regions of 2 to 8 cm^2 on repeated maps were targeted for ablation (73).

2) What are the optimal mapping requirements needed to detect clinically significant rotors?

    a. Issues with contact with multipolar basket catheters. Honarbaksh compared whole chamber panoramic mapping using multipolar basket catheters (MBC) Constellation catheters versus FIRMap catheters and found the LA coverage with FIRMap to be superior compared to Constellation catheters, 76.9 ± 12.9% vs. 50.8 ± 10.3%; $P < 0.001$) respectively. However, despite sizing basket catheters individually for patients, increasing LA area led to poorer coverage and contact (79). Similar result of poor LA coverage with the use of MBC was seen in another study, which provided only 54% of LA area was sampled (74). The resulting complication from this is the appearance of phantom rotors which might be misleading for the operators (80).

b. Issues with electrode density. A lower density of electrodes has been associated with less complex wavefronts and lower sensitivity of detection for rotational activities (81). In addition, false positives and false negatives of PS detection are possible depending on the density of electrodes and interelectrode distance (82-84). In a system where there are multiple co-existing rotors, Aronis et al showed through a silico study that the errors in localising rotors might increase by up to tenfold, suggesting higher density electrodes might be warranted in such scenarios (85).

c. Issues with phase mapping. A previous study has complex activation patterns during cardiac fibrillation that can produce false rotor detection such as during the interaction between wavefronts and line of functional/anatomical block. In this study, authors further suggested the combined use of activation maps and phase maps to improve the accuracy of rotor detection (86).

Not surprisingly, recent randomised trials involving patients with AF undergoing rotor ablation have so far yielded no additional clinical benefits. A recently published randomised controlled trial comparing FIRM-guided rotor ablation only versus PVI in PAF patients undergoing ablation, showed single procedure effectiveness of only 31.3% versus 80% after one year follow-up, with repeat catheter ablation procedure much more common in the FIRM guided rotor ablation group (45.8% versus 7.4%, respectively) (36). Findings from this study echo preliminary results from another randomised clinical study, the REAFFIRM trial, comparing PVI with FIRM-guided rotor ablation versus PVI alone, in patients with persAF which showed no difference in single procedure freedom from atrial tachyarrhythmias post ablation and need for repeat ablation procedure, comparing both groups (87).

1.3.3 Implications of delineating mechanisms maintaining AF

Crucially, identification of the exact mechanism driving AF would have significant implications in dictating catheter ablation strategies that would be beneficial for patients. In patients with paroxysmal AF, isolation of the pulmonary veins, with both focal activity and re-entry implicated, has been shown to have significant clinical efficacy (88). However, ablation strategy in patients with persistent AF is less well defined as mechanisms sustaining AF in these patients are still under debate. For instance, if AF is maintained by spatially stable rotors, then theoretically ablation of these areas would result in improvement in the clinical outcomes of patients. In addition, if AF is maintained by multiple randomly propagating wavelets, then additional ablation lines, be it posterior wall isolation or roof lines should be adequate to reduce critical atrial mass which supports these wavelets. However, the clinical efficacy of these strategies is yet to be consistently demonstrated, providing evidence that further work needs to be done to improve our understanding with this regard.

1.4 Progression of AF from paroxysmal to non-paroxysmal forms: Current understanding

The concept of "AF begets AF" first introduced by Wijffels et al in 1995 underlies the basis of contemporary understanding of the progressive nature of AF (89). Earlier animal studies have shown that as AF was artificially maintained in animals, there was a progressive increase in the duration of AF(89), associated with progressive structural (90) and electrophysiological remodelling in the left atrium (91). In humans, paroxysmal AF is usually a consequence of a local trigger or driver, with pulmonary veins focus being the major culprit (29). Progression of AF from a paroxysmal form to a permanent form occurs in the setting of progressive electrical, structural and functional remodelling as a consequence of the arrhythmia itself or progression of underlying cardiac structural disease or a combination of both (30). Importantly, as AF persists, the underlying physiology initiating and maintaining AF shifts from a focal trigger or driver to a more substrate-based driven AF promoting anatomical and functional re-entry with the appearance of extra-pulmonary vein triggers (31, 32).

Cohort studies have suggested that the rate of progression of AF (defined as the progression of AF from a paroxysmal to a non-paroxysmal form) is variable and highly dependent on a multitude of factors. In n=590 patients ≥70 years of age with no previous diagnosis of AF, the prevalence of subclinical AF (defined as episodes lasting ≥6 mins) detected on implantable loop recorders was 35% after a median of 40.2 (37.6 to 42.4) months of follow up, with progression to 24-hour AF episodes occurring in 16% of these patients. In a prospective observational study of n=468 patients with young-onset AF, defined as the occurrence of AF below the age of 60, mean age 46 ± 10 years, AF progression occurred at a rate of 2% per year (92). In the Euro Heart survey of n=1219 patients with PAF showed that progression of AF occurred in 15% of patients after one year (93) while the Canadian Registry of Atrial Fibrillation involving n=755 patients with PAF, with mean age 61.2 ± 14.2 years showed rates of AF progression of 8.6%, 24.3% and 36.3% at 1, 5 and 10 years respectively (94). In both these studies, significant predictors of AF progression included older age, underlying structural heart disease (left atrial dilatation, heart failure, valvular heart disease including aortic stenosis and mitral regurgitation), and other medical comorbidities including hypertension, chronic obstructive pulmonary disease and previous transient ischemic attack or stroke (93, 94). In the recently published AF-RISK study, a multi-center prospective observational study looking at AF progression and risk factors in n=392 patients with PAF and persAF, mean age 60 ± 11 years, showed much higher progression of AF from persAF to permanent (26%) compared to those with PAF to persAF (11%) after one year follow up. Concerningly, those with AF progression also experienced significantly higher rates of cardiovascular events and all-cause mortality compared to non-progressors (12.4%/year vs. 2.3%/year, $P < 0.001$).

Variability in rates of AF progression is even more evident in a subset of patients with implantable cardiac devices. Veasey et al showed in a retrospective study of n=356 patients with a pacemaker, mean age (±SD) 79.5±8.9 years, n=314 (88.2%) patients with PAF and n=42 (11.8%) patients with persistent AF. At the end of 7 years study period, he showed the majority of patients with AF continued to have predominantly PAF,

177/314 (56%) patients in PAF group at diagnosis continued to have PAF while 15/42 (365) patients with persAF at diagnosis was reclassified as PAF (95). Another retrospective study of n=323 AF patients with dual chamber pacemakers showed followed up for a mean duration of 3.2 years, these patients showed three different trajectories; low burden without progression, remitting-relapsing or progression of AF, with mean increase in AF burden of 0.34% per year, and age and heart failure being significant predictors of increased AF burden (95).

1.4.1 Clinical Outcomes in patients with atrial fibrillation progression

Despite the inherent limitations of temporal-based classification as discussed above, some studies have shown the importance of using the current classification of AF to predict clinical outcomes. The Fushimi AF registry involving n=4045 Japanese patients with AF (49% PAF) showed that patients with AF progression were associated with a significantly higher risk of ischemic stroke or systemic embolism and hospitalisations with heart failure when compared to patients with baseline PAF or sustained AF (persistent or permanent AF) after a median follow up period of 1105 days (96). The PREFER European registry of n=3223 AF patients with mean age of 72±9 years showed a higher incidence of heart failure in patients with baseline permanent AF and a higher incidence of coronary events in patients with AF progression after one year follow-up (97). Other available evidence to date lends support to the higher risk of stroke and systemic thromboembolism in patients with persAF in comparison to those with PAF (98-100). However, the impact of PAF and persAF on all-cause mortality remains uncertain, as some studies suggest higher mortality in patients with persAF (98, 101) while others have shown higher mortality in PAF (102, 103) or no difference between the two groups (104).

Importantly, the classification of AF into PAF or persAF has been an essential tool for clinicians to predict a successful outcome from an AF ablation procedure. Observational and randomised control trials have shown poorer clinical outcomes (freedom from atrial fibrillation, time to recurrence of AF) for patients

with persAF undergoing catheter ablation for AF (39, 105-107). The differences in clinical outcomes from ablation therapy in both these patient groups have led to the different strength of recommendations by the major cardiology societies with regards to indications for catheter ablation. For example, in 2016, the European Society of Cardiology recommended catheter ablation for symptomatic PAF as a Class 1A indication and a Class 2A level C for patients with symptomatic persAF(59) while similar levels of recommendations were also seen in 2014 American guidelines (58).

In addition, the clinical classification of AF has been used to dictate a physician's choice of ablation strategy. While pulmonary vein isolation (PVI) remains the cornerstone and effective ablation strategy in patients with PAF, lower success rates from PVI alone are seen in patients with persAF (107). The lower success rates from ablation therapy are hypothesised to be secondary to the substrate abnormalities that perpetuate AF in patients with persAF, rather than focal pulmonary vein triggers in PAF, which can usually be treated with PVI alone (108). However, substrate-based ablation strategies in patients with persAF have not been shown to improve clinical outcomes. To illustrate, the STAR AF 2 trial that randomised n=589 patients with persAF to PVI alone, PVI plus complex fractionated atrial electrogram ablation and PVI plus linear ablations across the left atrial roof and mitral isthmus showed no improvement to arrythmia-free survival between patient groups (39). Interestingly, a recent meta-analysis published by Salih et al looking at six studies (two randomised control studies and four cohort studies) involving 1334 patients with persAF comparing a strategy of PVI alone plus PVI plus posterior wall isolation (PWI) showed reduced recurrence rate of AF in patients receiving adjunctive PWI (PVI+PWI vs PVI alone, 19.8% vs 29.1%; RR, 0.64; 95% CI, 0.42-0.97; $P < 0.04$, respectively) after a mean duration of follow up of 21.6 months. More recently, results from the CAPLA trial was published, a study which randomised persistent AF patients undergoing first time catheter ablation to two strategies, PVI vs PVI plus PWI and showed no significant difference in 12-months freedom from arrhythmia free survival between both groups (109).

1.4.1.1. Clinical outcomes from ablation for paroxysmal versus persistent AF patients

Previous studies have suggested adverse clinical outcomes post catheter ablation in persAF patients post ablation, when compared to PAF patients. An earlier study by Oral et al involving n=70 AF patients showed significantly lower freedom from AF post segmental PVI in persistent AF (22%) versus paroxysmal AF patients (70%) after five months follow up(110). Further, in a published meta-analysis involving n=18657 patients with persistent and long-standing persistent AF, success (freedom from AF recurrence) from a single procedure off antiarrhythmic medications was approximately 43%, which increased to 69% with a second ablation procedure and with the use of antiarrhythmic therapy (111). In comparison, in paroxysmal AF patients, other studies have observed significantly higher rates of freedom AF recurrence post ablation of approximately 65-80% after a mean of 1.5 to 3 years follow up (112, 113). In a prospective population-based study involving n=3768 AF patients who underwent catheter ablation for AF, a higher risk of mortality (HR 1.74, 95% CI 1.15-2.63), hospitalisations from AF (HR 1.21, 95% CI 1.09-1.34) and periprocedural complications (HR 1.36, 95% CI 1.02-1.75) were observed in persistent AF patients after a mean follow up of 1329 days (114). However, an important observation was that catheter ablation in persistent AF significantly reduced AF-related hospitalisations after ablation, when compared to the period before ablation (HR 0.74, 95% CI 0.63-0.87).

However, in persistent AF patients, findings from a meta-analysis have suggested improved clinical outcomes in patients who received ablation therapy compared to medical therapy. In a meta-analysis performed by Chen et al, involving n=809 persistent AF patients randomised to ablation versus medical therapy, a significantly higher proportion of AF patients randomised to ablation therapy remained free from AF recurrence and were not without antiarrhythmic drugs, with also a lower requirement for electrical cardioversion and hospitalisations (115). Additional benefits were observed in persistent AF with heart failure, with an improvement in LVEF and quality of life scores, as measured by Minnesota Living with Heart Failure Questionnaire (115).

1.4.1.2. Ablation strategies beyond PVI in persistent AF patients remain ill-defined

In persistent AF patients undergoing ablation, the clinical utility of additional ablation strategies beyond PVI remains uncertain. The STAR-AF 2 study was a landmark clinical trial that randomised persistent AF patients to various ablation strategies: 1) PVI-only (n=67 patients) 2) PVI plus complex fractionated electrogram (CFAE) ablation (n=263 patients) and 3) PVI plus additional linear ablation (n=259 patients) (39). After 18 months follow up, freedom from recurrent AF was observed in 59% of patients who received PVI-only procedure, compared to 49% of patients with PVI plus CFAE ablation and 46% of patients with PVI plus linear ablations (39). Other randomised studies investigating the efficacy of additional ablation strategies in addition to PVI have observed conflicting results. In another study randomizing n=156 persistent AF patients to 3 groups: Group 1, PVI plus non-PVI trigger ablation, identified using stimulation protocols; Group 2, PVI plus empiric ablation of common sites for non-PV triggers including crista terminalis, superior vena cava, fossa ovalis); Group 3, PVI plus CFAE ablation followed up for 1 year, no incremental clinical benefits were observed with additional substrate modification when all 3 groups were compared (116). In another randomised study involving n=124 persistent and long-standing persistent AF patients randomised to PVI-only versus PVI plus additional substrate ablation (CFAE and linear ablations), no significant differences were observed in freedom from atrial tachyarrhythmia after one year follow up (54% versus 57%, P=0.86) (117). Findings from these studies were supported by the findings from a meta-analysis by Clarnette et al who previously observed a freedom from atrial tachyarrhythmias of approximately 43% after a single ablation procedure, regardless of strategy used (111). However, a recent study randomizing n=50 persistent AF patients to group 1, PVI-only versus group 2, PVI plus ablation of complex fractionated electrogram within low voltage mapping followed up for 24 months, showed higher one-year AF free survival in patients in group 2 compared to group 1 (84% group 2 versus 44% group 1, P=0.006) (118). Another prospective study involving n=85 persistent AF patients observed higher freedom from atrial tachyarrhythmia recurrence in patients who underwent PVI plus targeted ablation of low voltage areas (defined as <0.5 mV in AF), compared to patients who underwent PVI only procedure

(P<0.0001) (119). Similarly, a recently published meta-analysis suggested potential benefit of substrate modification targeting low voltage areas (LVA), defined as bipolar voltage <0.5 mV. In n=145 persistent AF patients (95 patients with PVI + LVA ablation versus 50 patients with PVI-only), Nery et al showed that freedom from atrial tachyarrhythmias was significantly higher in PVI + LVA ablation group, when compared with controls after 18 months follow up (P=0.022) (120).

However, while STAR-AF 2 suggest equivocal results from additional substrate modification beyond PVI, the study also observed that approximately 60% of persistent AF patients were responsive to a PVI-only procedure (39). Some studies have suggested the use of both peri-procedural and pre-procedural antiarrhythmic therapy to characterise a cohort of persistent AF patients that will be clinically responsive to a PVI-only approach. In a prospective study involving n=51 persistent AF patients, a positive clinical response to combined therapy of class 1 and class 3 antiarrhythmic before ablation predicted higher freedom from atrial tachyarrhythmia off drug therapy after fourteen months of follow up(121). Benak et al proposed a strategy evaluating response to pre-ablation amiodarone in persistent AF patients (122). In this cohort of persistent AF patients who successfully revert to sinus rhythm on amiodarone and received a PVI-only procedure, although persistent AF patients responsive to amiodarone therapy had a higher rate of re-do ablation procedures and shorter time to atrial tachyarrhythmia recurrence, approximately 70% of persistent AF patients remained free of atrial tachyarrhythmia recurrence after twelve months follow up (122). Similarly, in n=71 persistent AF patients pretreated with oral dofetilide for a median of 85 days before PVI, a decrease in P wave duration was observed, suggestive of electrical reverse remodelling with similar freedom from atrial tachyarrhythmia off antiarrhythmics was observed (76% versus 80% at 6 months and 70% versus 75% at 12 months, P=NS) when compared to control (paroxysmal AF patients) (123). In this cohort of patients, a decrease in P wave duration was an independent predictor of clinical success, adjusting for known AF-related risk factors (123).

Another retrospective case-control study observed significantly greater freedom from atrial tachyarrhythmia recurrence post PVI-only strategy in a cohort of persistent AF patients who clinically responded to pretreatment bepridil, compared to patients who failed to restore sinus rhythm with bepridil after a mean of eighteen months follow up (124). Interestingly, a recent retrospective study involving n=76 persistent AF patients has shown an association between failure of clinical response to bepridil pre-AF ablation with a higher burden of low voltage zones on electroanatomic mapping, suggestive of more advance LA remodelling in this cohort (125). More recently, Okawa et al also observed lower rates of AF recurrence in n=303 persistent AF patients who clinically respond to pre-treatment bepridil therapy, compared to non-responsive persistent AF patients after 36 months follow-up (22.2% versus 34%, P=0.022) (126)f. Adjusting for known AF-related risk factors, non-response to pre-ablation bepridil remained a significant, independent predictor of AF recurrence (HR 1.34, 95% CI 1.01-1.77, P=0.04) in this cohort of patients (126).

1.4.2 LA structural remodelling and atrial fibrosis

AF is associated with LA structural remodelling; comprising of i) at a macrostructural level, LA dilatation; and ii) at a microstructural level, with the formation of tissue fibrosis. Mechanistic studies have shown a crucial role of substrate size (LA enlargement) in the maintenance of AF (127). In clinical studies, LA size has been shown to be a significant predictor of development and progression of AF, and recurrence of AF after interventional procedures (cardioversion, surgical or percutaneous radiofrequency ablation) (128). Multiple modifiable and non-modifiable patient-related clinical factors predispose to atrial structural remodelling including older age, obesity, hypertension, congestive heart failure, structural heart disease, excessive alcohol use and obesity. At a microstructural level, a characteristic feature of LA structural remodelling is the formation of atrial fibrosis. The interplay of a multitude of complex mechanisms and pathways is implicated in the formation of atrial fibrosis including progressive atrial dilatation, oxidative stress and inflammation, calcium overload and activation of myofibroblast (129). In further detail, multiple

molecular pathways have been shown to predispose to the formation of atrial fibrosis including the presence of oxidative stress associated with an intracellular increase in the formation of reactive oxygen species during cardiomyocyte injury favouring profibrotic differentiation of fibroblasts into myofibroblasts and release of inflammatory cytokines (14, 130). Similarly, the release of inflammatory cytokines such as TNF-alpha, IL-1B, IL-6 and IL-2 which interact with fibrotic growth factors such as PDGH, TGF-B and matrix metalloproteinases (MMPs) will also result in atrial fibrosis (108). Other mediators of atrial fibrosis include the increased levels of angiotensin 2 resulting in activation of angiotensin 1 receptor with subsequent release of ROS and inflammatory cytokines (14), TGF-β mediated fibrosis (131), upregulation of connective tissue growth factor (132) and stimulation of platelet-derived growth factor associated with cardiomyocyte stress and injury (133).

1.4.2.1 Role of LA structures in AF: LA Posterior wall

Several anatomic and electrical properties in the LA posterior wall have been observed to contribute towards AF initiation and maintenance. Embryogically, LA posterior wall originates from similar cardiac tissue as that of the pulmonary veins (134). During the gestation period, the common pulmonary vein bifurcates and forms the left atrial posterior wall and pulmonary veins respectively (135). Electrically, cardiomyocytes in the LA posterior wall have larger sodium currents, lower potassium currents and a higher content of intracellular calcium within the sarcoplasmic reticulum (136). This translates to the cardiomyocytes in the posterior wall having a lower resting membrane potential, shortest refractory period compared to any other cardiac myocytes in other regions, and a short action potential duration (136). This increases the susceptibility of the posterior wall to atrial electrical misfiring. In addition, the LA posterior wall has the highest density of autonomic neurons and is also the site of pronounced epicardial fat deposition which contains ganglionic plexi, which predisposes to vagal-induced AF (137). A previous study utilizing cardiac computed tomography to measure epicardial fat volume in n=400 patients (n=200 patients with AF and n=200 patients without AF) have shown epicardial fat mass in the posterior wall as a

significant, predictor of AF, independent of other known cardiovascular risk factors (138). Electrically, cardiac regions adjacent to epicardial fat have also been shown to be regions with a lower voltage, and slower conduction with greater fractionation of electrograms (139). This may be a result of the paracrine action of the epicardial fat which releases proinflammatory cytokines triggers may have a direct effect on the electrophysiological properties of the myocardium adjacent to it (140). Finally, non-uniform orientation of myocardial fibres at the junction of the pulmonary veins and the LA posterior wall has also been hypothesised to result in non-uniform anisotropy leading to unidirectional block and localized re-entry, which results in AF initiation (141).

The LA posterior wall has also been implicated in the maintenance of AF. A study looking at the wall stress distribution in the LA in n=19 persistent AF patients showed the greatest wall stretch in the regions of the pulmonary vein ostia and the LA posterior wall, which also corresponded to regions of lower amplitude electrograms and lower voltage/electrical scar (142). Another study utilizing cardiac MRI to assess the spatial distribution of atrial fibrosis in n=113 AF patients referred for AF ablation showed preferential deposition of fibrosis in the posterior wall (143). The presence of fibrosis has previously been implicated in AF persistence given fibrosis results in conduction slowing, unidirectional block, and the formation of electrical reentry. Electrically, epicardial mapping of the posterior wall involving n=23 patients undergoing cardiac surgery showed significantly higher lines and burden of conduction delays, and conduction heterogeneity in this region in patients with a larger LA diameter (57 ± 4mm), when compared with patients with smaller LA diameter (39 ± 7 mm), $P<0.01$ (144).

Clinical outcomes from adjunctive posterior wall isolation in addition to PVI have been mixed. A meta-analysis involving n=1643 AF patients from seventeen studies (nine case series, four randomised controlled trials and four cohort studies) undergoing PWI procedure (with or without adjunctive PVI) showed freedom from atrial arrhythmia of 65% in all patients and 61% in persistent AF patients, which are similar to success rates observed in AF patients undergoing PVI only procedure (145). However, it may

be that only a subset of AF patients benefits from adjunctive posterior wall isolation. A meta-analysis by Salih et al which included n=1334 persistent AF patients (two randomised control studies and four cohort studies) showed a reduction in AF recurrence in patients who underwent adjunctive posterior wall isolation procedure with PVI compared to patients who underwent PVI only procedure (19.8% vs 29.1%; $P < 0.04$) (146). Finally, a recently published randomised clinical study randomizing persistent AF patients undergoing first time catheter ablation to PVI versus PVI plus PWI showed no additional arrhythmia free survival between both groups after 12 months follow up (109).

1.4.2.2 Role of LA structures in AF: Left atrial appendage.

LAA is an under-appreciated source of AF. Embryologically, LAA derives from the adsorption of the primordial pulmonary veins and their associated venous branches, which potentially could initiate AF, similar to the pulmonary veins (147). Structurally, the LAA relates to the coronary sinus via muscular sleeves and the left superior pulmonary vein by the ligament of Marshall, which contains sympathetic and parasympathetic fibres which could promote electrical firing from the LAA (148). Anatomically, the LAA is also connected to the interatrial septum and the right atrium via the Bachmann's bundle, an epicardial muscular structure and previous studies have shown that conduction slowing or block in the region of Bachmann's bundle could facilitate electrical re-entry and AF (149, 150). The presence of pectinate muscles and ridges within the LAA itself has been implicated in the formation of electrical re-entry and fibrillation-flutter-like activity, via continuous electrical wave breaks or attachment or detachment of the re-entrant electrical activity from the ridges (151). In addition, significant fibrotic depositions along with changes in conduction velocity and activation time have been observed in AF patients who underwent surgical ablation and LAA amputation, which could potentially be an arrhythmogenic nidus for AF (152).

An observational study performed in 2010 involving n=987 AF patients undergoing re-do AF ablation procedure showed the presence of LAA electrical firing to be in approximately 27% of patients, with LAA

being the sole source of arrhythmias with no pulmonary vein reconnections in 8.7% of patients and occurs predominantly in persistent AF patients. After a mean follow up of 12 months, freedom from atrial tachyarrhythmias was higher in patients who received focal ablation to the LAA or electrical isolation via ablation to the LAA ostium compared to patients who did not receive any ablation procedure to the LAA (74% versus 68% versus 15%, P <0.001, respectively) (153). Further clinical studies have suggested a potential clinical benefit from electrical isolation of the LAA. The BELIEF trial was the first randomised study recruiting n=173 long-standing persistent AF patients to two treatment groups: group 1 – wide antral PVI plus extensive non-pulmonary vein triggers versus group 2 – wide antral PVI plus extensive non-pulmonary vein triggers and LAA isolation. After one year of follow-up, freedom from atrial tachyarrhythmias was significantly higher in group 2 compared to group 1 (56% versus 28%, P = 0.001) (154). Further, a recently published propensity-matched meta-analysis including n=1092 non-paroxysmal AF patients showed significantly higher freedom from atrial tachyarrhythmia recurrence off antiarrhythmics in patients who underwent LAA isolation (68.9% in LAA isolation group versus 50.2% in non-LAA isolation group, P <0.001) (155). However, the risk of ischemic stroke remains an important clinical concern in patients who underwent electrical isolation of the LAA (156).

1.4.2.3 Role of LA structures in AF: Pulmonary veins

The pulmonary veins are considered the most important structures in AF pathogenesis. This is due to the certain unique anatomical and electrical properties of the pulmonary veins. Anatomically, longer pulmonary vein muscular sleeves, thicker pulmonary vein muscular tissue and larger pulmonary vein dimensions have been shown to contribute to pulmonary vein arrhythmogenesis (29, 157, 158). At a cellular level, the presence of pacemaker-like cells containing cardiac conduction tissue properties, which results in ectopic electrical firing within the pulmonary vein myocardium has been observed in multiple studies (159-161). Electrically, pulmonary veins have a shorter action potential duration and amplitude, compared to cardiomyocytes from other LA locations (162). This is due to inherent differences in ionic

currents in the pulmonary veins, particularly a lower density of inward rectifier current, lower density of transient outward potassium current, a lower density of L-type calcium current and a higher density of delayed rectifier current (162). In setting of rapid atrial pacing, Chen et al observed shortening of pulmonary vein action potential with a slow inward and transient outward currents and a larger transient inward and pacemaker current (163). Additionally, Chen et al also observed higher incidences of spontaneous pulmonary vein arrythmias in chronically paced canine models (164). Mechanistically, it is hypothesised that both electrical re-entry and triggered activity in the pulmonary veins play an important role in the initiation of AF.

Evidence supporting pulmonary vein electrical re-entry includes:

1) A shorter action potential, a depolarized resting membrane potential and slower upstroke velocity, considered conducive to micro-reentry in pulmonary vein muscular sleeves (165).
2) The presence of complex myofiber orientation in the pulmonary vein-left atrial junction, resulting in conduction slowing, unidirectional conduction block and micro-reentry (166).
3) Presence of complex fractionated electrograms in the pulmonary veins (167).
4) A shorter effective refractory period in the distal pulmonary vein than the pulmonary vein-LA junction, with conduction delay in the direction of pulmonary vein-LA junction to the distal pulmonary vein longer than the conduction delay from the distal pulmonary vein to the pulmonary vein-LA junction, providing a nidus for electrical re-entry (168).

Evidence supporting pulmonary vein automaticity includes: -

1) The presence of spontaneously firing pacemaker cells in the pulmonary veins (163).
2) The increased susceptibility of pulmonary vein myocytes to catecholaminergic stimulation, compared to cardiomyocytes in other atrial regions (169).
3) Abnormalities in calcium handling in pulmonary vein myocytes (170).

4) Increased triggered activity under different conditions including exposure to thyroid hormone, increased temperature and beta-adrenergic agonists (171-173).

Interestingly, electrophysiological properties of the pulmonary veins differ in AF patients with evidence of temporal chronicity, with larger LA size, with evidence of structural heart disease and LV systolic dysfunction. In a study performed by Seitz et al involving n=121 patients (paroxysmal AF, n=19; persistent AF, n=77; long standing persistent AF, n=25), passive pulmonary veins, defined as electrically silent pulmonary veins or pulmonary vein cycle length greater than LAA cycle length, was observed in 0% of paroxysmal AF patients, 40% persistent AF patients and 76% of patients with long-standing persistent AF. Additionally, passive pulmonary veins were also observed in patients with larger LA size and in those with evidence of structural heart disease (174).

Not surprisingly, pulmonary vein isolation has been the ablation strategy of choice for AF patients. In the seminal paper published by Haissaguerre et al in 1998, spontaneous ectopic firing was observed originating predominantly from the left followed by the right superior pulmonary veins, with 62% of patients who underwent electrical isolation of the pulmonary veins remained free from any recurrence of atrial tachyarrhythmias after 8 months follow up (29). However, clinical success from PVI ablation, particularly in persistent AF patients remains suboptimal (15).

1.4.3 Role of RA structural remodelling in AF

The role of right atrial (RA) remodelling in the maintenance and perpetuation of AF in humans is less well defined. Observational studies have suggested that AF is more prevalent in patients with pulmonary hypertension (PH), congenital heart disease and chronic lung diseases through their effects on the right heart (175-178). Interestingly, recent mechanistic studies in animals suggest changes in RA structure and formation of RA fibrosis might also play a role in the perpetuation of AF. In 2019, Hiram et al showed in an experimental rat model with PH, the inducibility of AF/atrial flutter was significantly higher in rat

models with PH compared to control animals (179). In addition, PH rat models demonstrated significantly higher RA fibrosis compared to controls with LA fibrosis occurring at a lesser extent (179). On a macrostructural level, PH rats also showed higher right ventricular mass and pressure with enlargement of the RA while optical mapping showed significant conduction slowing and rotor activity in the RA but not the LA (179). Similar reductions in RA voltage with increased low voltage areas have also been seen in a clinical study involving human patients with long-standing PH (180). Findings from another prospective observational study also suggested that structural RA changes might play a role in AF recurrence in n=168 AF patients with normal-sized LA (defined as a diameter less than 40 mm) who have undergone a pulmonary vein isolation procedure (181). The clinical significance of RA structural remodelling was also observed in a study by Wen et al in n=284 AF patients who underwent AF ablation. After 24 months of follow-up, RA diameter was predictive of AF recurrence only in patients with LA diameter ≥ 35 mm (HR 1.04, 95% confidence interval 1.007-1.082, p=0.021). Additionally, Kaplan-Meier survival curves have shown a significantly higher AF recurrence post-catheter ablation in AF patients with a RA diameter ≥ 35.5 mm compared to patients with RA diameter < 35.5 mm (182). Detailed structural analysis using CMR analysis of the RA in a prospective cohort study involving n=4967 participants in the Multi-Ethnic Study of Atherosclerosis (MESA) also revealed a significantly higher baseline RA maximum volume index (P=0.002) and RA minimum volume index (P<0.001), with associated lower RA functional parameters including lower baseline RA emptying fraction (P=0.02), lower peak RA global strain (P<0.001) and lower peak RA free-wall strain (P=0.049) in patients who developed AF at follow up compared to patients without AF (183). In addition, the presence of RA dilatation, as measured by RA volume index and RA dysfunction, measured by RA reservoir function have also been identified as independent predictors of postoperative AF development in n=142 patients who underwent coronary artery bypass graft. Electrophysiologically, the presence of a higher RA sample entropy (higher values indication random irregular electrical signals, lower values indicating regular periodic signals) and a positive RA to CS dominant frequency gradient has

been shown to predict poor acute and long-term clinical outcomes in n=70 persistent AF patients who underwent PVI and left-sided fractionated potential ablation in the coronary sinus and left atrium (184). The clinical importance of biatrial dominant frequency gradient has also been shown by Atienza et al who showed improved freedom from atrial tachyarrhythmias in AF patients who had abolishment of a left to right dominant frequency gradient after PVI and dominant frequency ablation in n=50 AF patients who underwent catheter ablation (185).

Other right-sided structural diseases including right-sided valvular dysfunction have been implicated in AF persistence. Masamichi et al observed severe tricuspid regurgitation along with a high B-natriuretic peptide (BNP) as independent predictors of AF recurrence post-PVI in this group of AF patients with normal sized LA (181). In addition, non-pulmonary vein triggers originating mainly from the superior vena cava, crista terminalis, coronary sinus ostium and right atrial septum were also seen more commonly in this subset of patients (181).

Clinical outcomes from surgical studies restoring sinus rhythm in AF patients suggest a potential benefit of targeted RA ablation. The Cox-Maze 4 procedure involves multiple surgical incision lines in both the left and right atrium. The RA surgical incisions in Cox Maze 4 include surgical lesions from the superior vena cava to the inferior vena cava and along the RA free wall to the tricuspid valve annulus. A long-term follow-up study involving n=59 persistent AF patients who underwent stand-alone Cox Maze 4 procedure showed that up to 84% of patients remained in sinus rhythm after seven years follow up, with 74% of patients off antiarrhythmic drug therapy (186). Similar observations were made in another earlier prospective observational study involving n=100 AF patients who underwent the Cox Maze 4 procedure (long standing persistent AF, 63%; paroxysmal AF, 31%). After 24 months follow-up period, freedom from AF was 90% with 84% of patients off antiarrhythmic medications. In the catheter ablation realm, mixed clinical successes from targeted RA catheter ablation for AF have been observed. For instance, Lin et al suggested the presence of a specific subgroup of AF patients with frequent paroxysmal AF episodes attributed to the

RA. These were patients with no atrial ectopic beats initiating AF, during isoproterenol infusion and atrial burst pacing. In n=13 patients with PAF secondary to RA substrate, targeted RA ablation to RA regions of conduction block, crista terminalis gaps and cavotricuspid isthmus resulted in freedom from atrial tachyarrhythmias in 85% of patients after 16 months follow up (187). Another observational study by Chen et al compared the clinical outcomes of persistent AF patients who underwent LA PVI plus LA complex fractionated atrial electrogram (CFAE) ablation versus LA PVI plus LA and RA CFAE ablation, in patients with non-terminating AF post LA ablation procedures. Chen et al observed at least half of these patients had a successful conversion to sinus rhythm or atrial tachycardia post RA CFAE ablation, with a predominance of RA CFAEs around the region of crista terminalis, followed by RA appendage and RA septum. Additionally, patients with significantly enlarged RA > 145 mm^3 had lower rates of AF conversion post RA CFAE ablation. After 30 months follow up, patients with AF termination during RA CFAE ablation had significantly less recurrence of AF, compared to patients with non-terminating AF post RA CFAE ablation (p=0.004) (188). However, other studies have also shown equivocal benefit from RA ablation. In a randomised study by Oral et al, n=85 patients with long lasting persistent AF who remained in AF post LA ablation were randomised to RA CFAE ablation versus electrical cardioversion. RA sites with significant CFAEs were observed in the region of the crista terminalis followed by the RA septum and superior vena cava. After six months of follow up, no significant differences were observed with regard to freedom from atrial tachyarrhythmia recurrence comparing both groups (189). It has been suggested that the presence of an AF cycle length gradient will help determine a patient's clinical response to LA only or LA plus RA ablation.

Mechanistically, evidence suggests that in most AF patients, a left-to-right dominant frequency gradient exists, implying that the LA is the "driver" of AF in the patients. This may have implications in terms of catheter ablation strategy, i.e.: a targeted LA ablation versus adjunctive RA ablation in addition to LA ablation. In canine models of acute (AF induced by rapid atrial pacing) and chronic AF (AF created after six

weeks of atrial pacing), AF cycle length was significantly shorter in the LA compared to the RA in both models of AF, with a higher degree of disorganization of electrical conduction in the LA compared to the RA in the chronic AF group (190). For instance, using dominant frequency analysis, Sanders et al observed a larger distribution of dominant frequency sites around the pulmonary veins compared to the coronary sinus and RA in paroxysmal AF patients, gradient of which diminished in persistent AF patients, highlighting the potential crucial role of pulmonary veins as an ablation target in paroxysmal AF patients (191). Similarly, an observational study by Lazar et al involving n=31 paroxysmal and persistent AF patients showed the presence of a dominant frequency gradient, which is highest in the pulmonary veins followed by the coronary sinus and RA in paroxysmal AF patients, but no significant gradients comparing all these sites in persistent AF patients (192). A few hypotheses have been proposed to contribute to this left-to-right atrial gradient. Firstly, it has been observed in Langendorff-perfused sheep hearts that the concentration of acetylcholine-activated potassium channels was greater in the LA compared to the RA, making the LA more susceptible to sustaining unstable re-entrant circuits (193). Secondly, atrial structural remodelling including fibrotic depositions in setting of aging, diastolic dysfunction has been observed to affect the LA more than the RA (194-196). Finally, the LA is also adjacent to other electrically active structures including the pulmonary veins and posterior wall which consequently results in RA being a passive chamber in AF (197).

From a therapeutic perspective, loss of left-to-right gradient post-ablation has been associated with improved clinical outcome. Atienza et al showed that a reduction in dominant frequency in the LA and RA, accompanied by loss of left to right gradient was associated with improved freedom from atrial arrhythmias in an observational study involving n=50 AF patients who underwent both PVI plus dominant frequency ablation. In that study, a significant dominant frequency gradient exists between the pulmonary veins and the LA and RA in paroxysmal AF patients, which decreases in magnitude in persistent AF patients. Another clinical study by Hocini et al involving n=148 persistent AF patients, a parallel increase

in biatrial AF cycle length during LA only ablation predicted excellent clinical outcomes after 40 months follow up. However, in 30% (n=44) patients with a right to left cycle length gradient after LA ablation, AF cycle length prolongation in the RA with adjunct RA substrate modification particularly around the region of RAA, anterior RA and lateral RA predicted improved clinical outcomes compared to patients without a cycle length change during RA ablation. Further atrial structural characterisation revealed the presence of enlarged RA size in AF patients with a right to left AF cycle length gradient. Findings from this study suggests a subset of patients with electrophysiologically significant RA substrate that may clinically respond to additional RA ablation (198).

1.4.3.1 Role of RA structures in AF maintenance: Crista terminalis and pectinate muscles

The crista terminalis (CT) is a fibromuscular ridge that arises from the atrial septum medially, courses the orifice of superior vena cava anteriorly and descends postero-laterally to the ostium of the inferior vena cava (199). The CT divides the smooth portion of the RA from the pectinate muscles (PM), which branches out at right angles and extends anterolaterally. From an electrophysiological standpoint, cardiomyocytes in the region of CT have gap junctions located at the poles of cells leading to a longitudinal or end to end electrical connection (200). This results in a preferential conduction in a longitudinal fashion, and conduction velocities up to 10 times greater in the longitudinal direction compared to a transverse conduction, when compared to cardiomyocytes in other myocardial regions (201). Multiple atrial tachyarrhythmias have previously been associated with the CT. For instance, typical atrial flutter which is a macro-reentrant atrial rhythm uses the CT as an anatomical electrical barrier to prevent conduction between the RA lateral and posterior wall, and because of the unique arrangement of the gap junctions as discussed earlier, provides the fastest electrical conduction during atrial flutter in a longitudinal direction with a line of block in the transverse direction. Similarly, other studies have also implicated the clinical significance of the CT in majority of atrial tachycardias arising from the RA (202, 203). However, studies looking at the role of CT have been limited. During onset of AF, it has been observed that a line of

functional conduction block develops across the CT, but whether this line of block serves to initiate or maintain AF, or just a passive consequence of fibrillatory conduction remain poorly defined (204).

Similarly, RA pectinate muscles (PM) have been implicated in the initiation and maintenance of AF. In n=10 isolated canine right atrial tissue models, Wu et al observed that a large PM ridge served as an anatomical substrate which initiates intra-atrial reentry and anchors re-entrant circuits (205). In comparison to RA areas without PM, the mean lifespan and cycle length of re-entrant circuits in PM areas are significantly longer (205). Additionally, electrical propagation was slower in the RA PM regions, with non-uniformity of conduction velocity across a large PM and a critical thickness of PM was needed for the anchoring of re-entrant circuits (205). Anchoring of re-entrant circuits determined whether the underlying rhythm is atrial flutter (where spiral waves remain anchored to PM) or AF (spontaneous detachment of spiral waves from PM, observed to be precede by cycle length oscillations) (205). Similarly, in another study involving n=37 patients undergoing cardiac surgery for multiple reasons, electrophysiological analysis of cardiac specimens obtained from PM revealed progressive age-related loss of electrical coupling in these region resulting in tissue anisotropy and formation of electrical re-entry (206). Further, another study using pectinate muscle network derived from isolated sheep right atrium showed that the presence of extensive branching of the PM could result in electrical activation delays, intermittent conduction block and fibrillation-like electrical conduction, even in setting of regular periodic electrical inputs (207).

1.4.3.2 Role of RA structures in AF initiation and maintenance: Superior vena cava

Ectopic firing from the SVC-RA junction has been hypothesised to be one of the potential origins of non-pulmonary vein triggers in AF (208). Anatomically, this region appears similar structurally to the pulmonary vein-LA junction. In the pulmonary veins, myocardial sleeve extensions result in automaticity and rapid atrial conduction, which acts as a trigger for AF (209). However, properties of myocardial

extensions into the SVC differ from pulmonary vein muscular sleeves as they lack expression of rapidly conducting gap junctions, but with a higher predilection for automaticity secondary to both the presence of phase 4 depolarisation and triggered activity (209, 210).

Results from n=25 autopsied human hearts show a high prevalence of myocardial sleeve extensions from the RA into the SVC (75%), with a mean length of 14 mm up to 47 mm (211). The length of the myocardial sleeve extensions from the RA into the SVC has previously been shown to be a significant predictor of SVC firing in patients with AF (212). Another study observed the presence of SVC arrhythmogenicity in patients with SVC myocardial sleeves greater than 30 mm and in patients with large SVC potential > 1 mV (213). The location of the SVC-RA junction which lies near the SVC-Aorta ganglionic plexus, may also account for its role as an initiator for AF. A previous study has shown that stimulation of the SVC-Aorta ganglionic plexi triggered episodes of AF, by means of shortening of the effective refractory period and could be treated by ablation of the SVC-Aorta ganglionic plexi (214).

However, the clinical utility of empiric SVC isolation in addition to PVI remains poorly defined. Ejima et al performed a prospective study in n=186 paroxysmal AF patients, where n=93 patients received PVI plus SVC isolation, if SVC triggers were identified, and another n=93 patients received PVI plus empiric SVC isolation. After a mean follow up of 27 ± 12 months, recurrence of atrial tachyarrhythmia was significantly lower in patients who received empiric SVC isolation in addition to PVI (44% versus 23%, P=0.035) (215). However, conflicting clinical outcomes were observed in other randomised studies. In a randomised study involving n=106 paroxysmal AF patients randomised to either PVI or PVI plus SVC isolation, no significant differences in freedom from atrial tachyarrhythmias were observed after 12 months follow up (92% PVI versus 94.2% PVI plus SVC isolation, P=0.73) (216). Similarly, another study involving n=100 paroxysmal AF patients randomised to PVI versus PVI plus SVC isolation showed no significant differences in atrial tachyarrhythmia recurrences after a longer follow up period of 15 ± 8 months (18% PVI versus 12% PVI plus SVC isolation, P=0.06) (217). In addition, Corrado et al suggested that clinical benefit from adjunctive

SVC isolation may only be seen in a subset of AF patients (218). In n=320 AF patients involving patients with paroxysmal, persistent, and permanent AF who underwent SVC isolation plus PVI procedure versus PVI only procedure, only a subset of patients with paroxysmal AF had significantly higher freedom from atrial tachyarrhythmia recurrence after 1 year follow up when both treatment groups were compared (PVI 77% versus PVI plus SVC isolation 90%, P=0.04) (218).

1.4.4 Histological evidence of myocardial fibrosis in atrial fibrillation

Histological studies in both animals and humans have suggested a potential role of fibrosis in the maintenance and perpetuation of AF. Two distinct histopathological subtypes of fibrosis have been observed. Reparative fibrosis occurs in the setting of cardiac injury with the formation of fibrous scar tissue replacing necrotic myocardium while “reactive” fibrosis with the deposition of extracellular matrix proteins and collagen in the interstitial space surrounding the cardiomyocytes or vascular areas (14). In goat models with sustained AF induced by rapid atrial pacing for up to 23 weeks, revealed a significant increase in the size of cardiac myocytes associated with myofibril loss, glycogen accumulation with changes in mitochondrial shape and size and fragmentation of the sarcoplasmic reticulum (90). Tachy-paced animal model studies have subsequently revealed higher degrees of glycogen, collagen and atrial fibrosis in the AF group compared to controls (219, 220). Another study by Verheule et al. in goat models with AF maintained for a short term (ST, three weeks) versus long term (LT, six months) also revealed significantly larger endomysial fibrosis in the LT group, predominantly in the epicardial layer (increased distance between myocytes within bundles), corresponding to more complex epicardial wavefront activation on optical mapping in the LT group (221).

Histological analysis of human atrial myocardium has also revealed higher amounts of fibrosis in patients with AF. A post-mortem analysis of n=30 patients divided into three equal groups 1:1:1 (patients without a history of AF vs paroxysmal AF vs persistent AF) with similar clinical profile revealed up to threefold

fibrosis associated with inflammatory cell infiltrates (lymphomononuclear cells) in patients with AF compared to those without AF, and similarly, higher in those with persistent compared to paroxysmal AF (222). Similar findings of increased fibrosis with inflammatory cells infiltration in the atrial wall were also seen in a group of patients with lone AF (223). Previous further analysis of the extracellular matrix obtained from cardiac biopsy suggested an increase in both collagen type 1 and collagen type 3 in patients with lone AF, and in patients with AF and mitral valve disease compared to patients in sinus rhythm and mitral valve disease, highlighting the central role of atrial fibrosis in the maintenance and perpetuation of AF (224).

1.4.5 Spatial Distribution of left atrial fibrosis

Multiple studies have also shown a spatial and preferential distribution of LA fibrosis in AF patients, depending on their AF persistence. This is important as a previous study has shown a predilection of reentrant drivers in AF to areas of LA fibrosis, which could in future, potentially guide ablation strategies (225). For instance, Higuchi et al showed in n=160 AF patients undergoing ablation, the highest LGE coverage was found to be in the posterior side of the left inferior pulmonary vein (LIPV) antrum, with a greater spread of fibrosis on the anterior and posterior wall in patients with persAF compared to PAF (226). Similar findings were seen in other studies; a retrospective study by Lee et al looking at n=195 AF patients, also showed a significant presence of fibrotic segments in patients with persAF, particularly in the LIPV antrum while Benito et al also showed a preferential fibrosis of LA around the posterior wall of LIPV in n=113 AF patients undergoing AF ablation (143). Another study by Aparina et al compared the distribution of LA fibrosis between 3 groups of patients (n=60 patients with AF, n=30 patients with hypertension but no AF, and n=28 healthy volunteers). In the AF patients, 3 different spatial distribution of LA fibrosis were identified, with a predominance of preferential involvement of the pulmonary vein region (52.2%) followed by uniform fibrosis across all LA walls (32.6%) and on the posterior LA wall (11.2%). In patients with hypertension but no AF, predominant uniform fibrosis was seen in all LA walls is

seen in 44.4% of all patients followed by pulmonary vein region (27.7%), posterior LA wall (16.7%) and lower part of LA wall (11.2%). Finally, in healthy volunteers, the predominant area of fibrosis was at the lower part of LA wall adjacent to the mitral valve annulus (90%) (227). Histopathological results from studies charactering atrial fibrosis in AF patients have also shown preferential fibrosis around the pulmonary veins, particularly the LIPV and posterior wall compared to other regions in the LA (222, 228). The reasons behind this spatial distribution of fibrosis in AF patients are interesting. Hunter et al showed in n=19 patients with persistent AF, evidence of high levels of LA wall stress was found around the ostia of the pulmonary veins (left higher than right) followed by the LA appendage ridge, posterior wall and roof, which corresponded to areas of low voltage and electrical scar (142). In addition, Benito et al hypothesized that given the close proximity of the LIPV to the descending aorta, aortic pulsatility may play a role in fibrosis in this region (143).

1.4.6 Atrial fibrosis as a substrate for arrhythmia

From a mechanistic standpoint, the association between fibrosis and AF may be explained by several potential mechanisms: -

1) Slowed intercellular electrical wave propagation due to the presence of interpolating collagen strands between cardiomyocytes (229)
2) Formation of unidirectional conduction block due to anatomical barriers formed by areas of fibrosis (229)
3) Localised micro-reentry associated with patchy fibrosis (230)
4) Increased automaticity of cardiomyocytes secondary to the presence of hetero-cellular gap junctions between cardiomyocytes (231)

5) The paracrine function of fibroblasts resulting in slowing of conduction velocity and increased cellular refractoriness (232)

1.4.7 Evidence linking atrial fibrosis and re-entrant activity.

Fibrotic regions in the atrium may result in shortening of action potential duration and slowing of conduction velocity (an effect which increases with dense fibrosis), with incremental chaotic wavefront propagation, with multiple unstable local re-entries and zig-zag propagation as fibrotic density increases (233). Results published from clinical studies have reported clustering of re-entrant activities during atrial fibrillation around zones of atrial fibrosis. A positive correlation between the extent of LGE and the number of re-entrant activity (REA) with clustering of REA around zones of atrial fibrosis was observed in n=41 patients with persistent AF (234). Similar findings were observed in computational atrial models deriving areas of fibrosis from CMR LGE showing spatial predilection of REA to areas of atrial fibrosis, particularly at the boundaries between fibrotic and non-fibrotic tissue (225, 235), with influence from atrial tissue variation of action potential duration, electrical wavelength and conduction velocity (235, 236). In non-fibrotic areas, REA clusters around areas with a high action potential duration gradient (such as the LA-pulmonary vein junction) (236) and in areas with a prolonged long action potential duration (236, 237). Interestingly, using percolation models of sinus rhythm, paroxysmal and persistent AF, Falkenberg et al. also showed an increasing difficulty of termination of RE with ablation as the depth of RE through the atrial tissue wall increases with the degree of atrial fibrosis, as AF progresses from PAF to persAF (238). This finding may explain the lower success rates with AF ablation in those with persAF compared to those with PAF.

1.4.8 Classification of atrial fibrillation based on fibrosis.

The currently used clinical classification of AF proposed by Gallagher et al highlights three clinical categories of AF based on duration of AF (paroxysmal, persistent and permanent) (55). However, there is

no evidence to support the 7-day cut off, an arbitrary duration used to differentiate the paroxysmal from non-paroxysmal forms of AF (55). Crucially, this clinical classification of AF is used by physicians to choose between rate versus rhythm therapy and to dictate whether an interventional therapy would be appropriate for their patients. Recently, Kottkamp et al. introduced the term fibrotic atrial cardiomyopathy (FACM) to differentiate paroxysmal AF patients, where pulmonary vein (PV) triggers are the main initiators of AF, with persistent AF patients, where a self-perpetuation of AF leads to further structural remodelling and fibrotic changes within the atrium (239). Variable degrees of FACM were described by the authors, from those with mild to severe fibrosis (FACM 1-3) although this is purely descriptive and no cut-off threshold was proposed in this paper (239). In 2016, the EHRA/HRS/APHRS/SOLAECE released a consensus statement on atrial cardiomyopathy defining it as "any complex structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations" and proposed four different histopathological classifications, based on LA substrate remodeling in patients with AF. This includes Class 1 – cardiomyocyte dependent, occurring in patients with lone AF, diabetes mellitus, or patients with genetic predisposition, Class 2 – fibroblast dependent, occurring in smokers and the elderly, Class 3 – mixed cardiomyocyte-fibroblast, occurring in patients with heart failure and valvular disease, and Class 4 – non-collagen deposit group, which occurs primarily in patients with infiltrative diseases such as atrial amyloidosis or granulomatosis. However, prognostic implications of each of these classes are not well defined, and the use of this classification in clinical practice is cumbersome as it involves invasive cardiac biopsy (240).

Perhaps the most important study correlating the extent of atrial tissue fibrosis and clinical outcomes post catheter ablation was demonstrated by the DECAAF study in 2014. In this multicentre, prospective observational study, n=260 AF patients who had atrial fibrosis quantification by LGE-CMR were followed up for around one year. Atrial fibrosis burden was divided into four stages; stage 1, <10% of the atrial wall, stage 2, ≥10% but <20% of the atrial wall, stage 3, ≥20% but <30% of the atrial wall and stage 4, ≥30% and

patients were followed up for 325 days (241). Arrhythmia recurrence increased with higher stages of atrial fibrosis, with AF patients with stage 1 fibrosis associated with 15.3% (95% CI, 7.6%-29.6%) risk of arrhythmia recurrence and stage 4 fibrosis associated with arrhythmia recurrence of up to 69.4% (95% CI, 35.6%-57.5%) (241). In addition, further analysis of DECAAF also showed that in n=177 AF patients who underwent LGE-MRI post-AF ablation, the burden of residual atrial fibrosis (defined as pre-ablation atrial fibrosis not covered by ablation scar), but not PV encirclement was an independent predictor of arrhythmia recurrence at the end of 325 days follow-up (242). More recently, results from the DECAAF 2 study was published, a clinical study which randomised persistent AF patients to two ablation strategies; PVI plus MRI guided atrial fibrosis ablation versus PVI alone, and showed no difference in arrhythmia free survival between both groups after 12 months follow up (243).

Notably, the presence and extent of LA fibrosis have previously been correlated with adverse clinical outcomes in patients with AF. The association between LA fibrosis and stroke, a feared complication of AF has been described. A retrospective study by King et al. looking at n=1228 AF patients who underwent LGE-CMR imaging for LA fibrosis quantification showed a positive correlation between the extent of fibrosis and major adverse cardiovascular events (MACE), driven primarily by increased in the incidence of strokes and TIAs (HR 3.94; CI 1.72 to 8.98) (244). In patients undergoing trans-esophageal echocardiogram before AF ablation, a greater extent of LA fibrosis of >20% was also associated with the presence of LA appendage thrombus and spontaneous echo contrast (245). In another cohort of patients undergoing AF ablation, a greater extent of pre-procedural LA fibrosis has been previously associated with an increased likelihood of recurrent arrhythmia and increased need for repeat ablation procedures, after medium and long-term follow up (241, 246-248). Given observational evidence linking presence and extent of fibrosis with MACE and poorer clinical outcomes post-ablation, the determination of AF structural phenotype with the degree of LGE may be useful to guide decision-making regarding AF patients who will benefit the most from an ablation procedure. Three clinical methods of fibrosis detection include

the non-invasive direct detection of fibrosis using CMR, indirect non-invasive detection of fibrosis using LA strain and invasive detection of fibrosis using electroanatomic mapping, with its use and limitations described below and summarized in Figure 1.

1.5 Identification of atrial fibrosis

1.5.1 Direct detection of left atrial fibrosis using cardiac magnetic resonance imaging

The presence of LGE on CMR has been used to characterize and quantify the extent of replacement fibrosis in the LA in patients with AF (249, 250). Early histopathological validation of LGE CMR has been exclusively in the ventricle of large animal models and the abnormalities seen represent areas of necrosis and/or replacement fibrosis (251) In the left atrium, detection of LGE as a surrogate for LA fibrosis using CMR has been both cross-validated with histological studies (252) and areas of low voltage zones (LVZ) on electroanatomic mapping (249, 253). However, compared to echocardiographic and electro-anatomical mapping methods, CMR is more likely to offer a comprehensive assessment of underlying atrial fibrotic substrate as it is less likely to be influenced by wall tracing errors (through echo derived strain and strain rate) or lack of tissue contact (electro-anatomical mapping) (254, 255). Visualisation of fibrotic areas in the LA relies on alterations in Gadolinium washout in these areas compared to the healthy myocardial tissue, with accumulation of Gadolinium in areas where fibrosis is present resulting in fibrotic regions appearing as hyper enhanced areas while normal healthy tissue appearing non-enhanced (i.e. dark) (256). The extent of LA fibrosis may be quantified using the Utah classification system proposed by Marrouche et al., with increasing severity of fibrosis from stage 1 to 4; stage 1 (<10%) of the atrial wall; stage 2 (10%; <20%); stage 3 (20%; <30%), and stage 4 (≥30%) (241). While CMR is an attractive option to determine the extent of LA fibrosis in AF patients, some limitations must be acknowledged: -

1) Lack of a universal standardized approach to analysing LA fibrosis. Multiple methods have been previously used including:

a. Manual or semimanual segmentation of the LA walls from CMR LGE images (257)

b. Definition of LA fibrosis as a signal intensity distribution of 2 to 4 standard deviations above mean signal intensity arising from normal myocardium (241, 245, 258).

c. Use of image intensity ratio (IIR), which normalizes the LA wall intensity to the mean blood pool intensity. However, there is no agreement on the IIR threshold for fibrosis to date (253).

2) Accurate analysis of LA fibrosis largely depends on the quality of the CMR LGE images. A study by Margulescu et al. revealed 25% of the CMR LGE analysis had to be excluded for varying reasons including issues with ECG-triggered algorithm leading to inaccurate images of LA wall, insufficient LV myocardial suppression and non-uniformity of gadolinium distribution in the LA (259). Other causes of poor image quality, including:

   a. Thin atrial walls, leading to difficulty differentiating between transmural versus partial-thickness fibrosis in the setting of limited spatial resolution(257).

   b. Dosage of contrast agents (260).

   c. Patient factors, including haematocrit and body mass index (BMI) (260).

   d. Field strength (260).

   e. Lower sensitivity for fibrosis detection in the setting of elevated heart rates (261).

   f. Presence of arrhythmia leading to issues with LA wall artefacts (257).

Despite its limitations, a recent study looking at inter and intra-observer reproducibility of CMR LGE quantification of LA fibrosis showed excellent agreement between experienced and non-experienced reading physician with a coefficient of variation of <10% and intraclass correlation coefficient (ICC) of

>0.71. Similarly, high ICC for detection and quantification of LA fibrosis was also seen in other studies, in both patients with paroxysmal and persistent AF (245, 252, 258).

The widespread use of CMR is significantly limited by the lack of CMR tool itself in some centres or lack of experienced centres in performing LA fibrosis analysis (261), hence indirect assessment of LA fibrosis using loss of LA function as a surrogate for fibrosis measured using LA strain or detection of low voltage zones using electroanatomic mapping during ablation might be a more attractive option in the detection and quantification of fibrosis, as discussed below.

1.5.2 Indirect detection of left atrial fibrosis using loss in left atrial function as a surrogate.

In normal cardiac physiology, LA plays an essential role in left ventricular filling and contributes up to 30% of cardiac output (262). During ventricular systole, the LA functions as a reservoir; the LA fills and stretches as it stores blood drained from the pulmonary veins, leading to a positive LA strain that peaks just before the opening of the mitral valve (MV). Early in ventricular diastole, the LA functions as a passive conduit; the opening of the MV leads to passive LA emptying into the left ventricle, which results in a decreased atrial strain until it reaches a plateau, corresponding to LA diastasis. Late in ventricular diastole, the LA functions as an active booster pump; LA contraction, also corresponding to atrial systole, which further contributes to 15-30% of LV filling (263). Changes in loading conditions affect LA function (264). For instance, pathological increase in LA afterload occurs in the setting of increased LV filling pressures and LV diastolic dysfunction seen in cardiovascular conditions such as hypertension and aortic stenosis (265). In these patients, a reduction in LA conduit function is observed, which is compensated by an increase in LA contraction to maintain optimal LV filling. Increased LA contraction in these scenarios also increases LA preload, by increasing the backward flow of blood into the pulmonary venous system resulting in LA dilatation (265). Progressive LA dilatation eventually results in progressive LA failure, once threshold of LA fibre length is reach, analogous to the Frank-Starling mechanism (264).

The functional decline of the LA has been shown to precede the diagnosis of AF. A recent study by Lim et al. looked at cardiac imaging predictors of AF development in n=132 patients from the Multi-Ethnic Study of Atherosclerosis free of cardiovascular disease at baseline after a mean follows up of 3.8 ± 0.9 years. In this study, an annual decrease in LA emptying fraction and strain and a more significant annual increase of LA volume were identified as predictors of the development of AF (266). Another earlier prospective study by Abhayaratna et al. also showed the predictive value of lower LA emptying function, measured by LA reservoir for new-onset AF or atrial flutter in n=574 patients, mean age of mean age 74 ± six years, independent of LA volume after follow up for 1.9 ± 1.2 years (267). Similarly, Hirose et al. also showed in a prospective study of n=580 patients with no history of AF at baseline, using a cutoff value of LA emptying fraction ≤20%, the sensitivity and specificity for the prediction of new-onset AF was 88 and 81%, respectively (268).

LA strain is essentially a measure of myocardial deformation. The clinical utility of LA strain and LA strain rate in assessing LA mechanics and deformation is well established, and its use in the functional assessment of LA is rapidly evolving (269). This can be measured using 2D speckle tracking echocardiography (STE), a robust and established method to assess LA strain and strain rate (269) with its feasibility and reproducibility previously validated in multiple studies (270, 271). In AF patients, lower LA strain has been linked to a higher burden of LA fibrosis (272, 273) with regional LA strain significantly lower in LA areas with LGE observed on CMR, indicating areas of LA fibrosis compared to LA areas without LGE (274) while another retrospective study looking at n=971 AF patients enrolled in the ENGAGE AF-TIMI 48 trial, showed progressive reduction in LA emptying fraction and increase in LA volume index as AF subtype progresses from paroxysmal, to persistent and permanent, respectively. However, there are some limitations to the use of echo-derived LA strain and strain rate as a fibrosis surrogate, and these include: -

1. LA strain is not reproducible across different vendor platforms (275).

2. Lack of established and accepted average reference values for LA strain (276).

3. LA strain is affected by different loading conditions (277).

4. The methodology to obtain LA strain measurements require standardization. Current recommendations by European guidelines suggest using apical-four chamber views for all LA strain assessments with the option of obtaining apical two-chamber views for biplane LA strain calculation (269).

5. Technical challenges during LA image acquisition. For example, LA strain is affected by the presence of atrial septal aneurysms (278). Also, the inclusion of the LA roof in image analysis has been debated as it often includes the pulmonary venous structures with transverse muscular bundles in the region providing no additional information on LA longitudinal deformation (256).

6. Lack of standardization of the ECG reference point for LA strain assessment. Currently accepted technique for LA strain analysis includes at the onset of a P wave or onset of QRS (269).

7. Thin LA walls lead to poor LA wall tracking, especially in patients with enlarged LA (254).

1.5.3 Indirect detection of left atrial fibrosis using the presence of low voltage zones on electroanatomic mapping

Another method for the detection of LA fibrosis in AF patients is the presence of low voltage areas (LVA) on electroanatomic mapping during catheter ablation for AF. Electroanatomic voltage maps are created using thousands of voltage points (bipolar electrogram amplitude, which is the voltage difference between two neighbouring unipolar electrograms) projected onto the atrial shell (279). From a physiological standpoint, low voltage electrograms measured in these fibrotic areas have been a result of discontinuous conduction and poor tissue coupling in the presence of non-uniform anisotropic tissues (60, 280, 281).

Although there is a lack of histological evidence correlating LVA with atrial fibrosis in humans, LA LVA has previously been shown to correspond to non-invasively detected areas of fibrosis quantified using LGE-CMR (249, 282). Besides, Zghaib et al. had also previously shown in n=26 AF patients undergoing ablation, each unit increase in local image intensity ratio (LGE-MRI technique which normalizes mean myocardial intensity to mean intensity of blood pool, per cardiac sector) led to a 57% decrease in bipolar voltage, with an IIR >0.74 corresponded to a bipolar voltage of <0.5 mv (283). Not surprisingly, an increase in the left atrial stiffness index (ratio of E/e' to LA peak strain) was also seen in these zones of LVAs, strengthening the link between LVAs, atrial fibrosis and the loss of atrial function (284).

From a clinical standpoint, the increasing burden of LVA detected on electroanatomic mapping has been associated with adverse clinical outcomes. In n=160 patients, 53% with paroxysmal AF, patients with LVA had lower 12-month arrhythmia-free survival compared to those without LVA in those with paroxysmal (38% vs 76%; *p*=0.002) and persistent AF (27% vs 61%; *p*=0.015). Interestingly, patients with persistent AF with no LVA had similar arrhythmia-free survival in comparison with patients with paroxysmal AF (61% vs 67%, respectively; *p*=0.42). Higher rates of arrhythmia recurrence in patients with LVA undergoing pulmonary vein isolation have also been described by other investigators (285, 286). At the same time, another study has also shown recurrence of arrhythmia in patients with LVA is also more likely to be organized atrial arrhythmia than AF itself (287). Also, another study has shown a significant association between LVA and clinically manifest and subclinical silent cerebral ischemia detected on cerebral delayed-enhancement MRI in 200 patients with AF undergoing ablation, even after adjustment for CHA2DS2-VASC score (288). This may be attributed to a reduced left atrial appendage flow velocity with the presence of LVZ, particularly on the LA anterior wall, which could subsequently lead to thrombus and cardioembolic complications (289).

Limitations to the use of LVZ on electroanatomic mapping include:

1) It is unclear what the threshold of low voltage for the definition of abnormal atrial tissue should be. While traditionally, LVA is defined as bipolar voltage amplitude < ≤0.5 mv while scar tissue is defined as bipolar voltage amplitude ≤0.05 mV (290), this has not been histologically validated in atrial tissue biopsy. Other studies have used different cut-offs for LVA detection threshold (291, 292)

2) It is unclear whether voltage maps should be created in sinus rhythm or AF. A recent study by Qureshi suggested that mean AF voltage correlates better with delayed-enhancement CMR detected atrial fibrosis with a sensitivity and specificity of 75% and 79% respectively using a threshold of 0.35 mv in comparison with mean sinus rhythm voltage and delayed-enhancement CMR detected atrial fibrosis, sensitivity and specificity of 63% and 67%, respectively (291). If the substrate is mapped in AF, then a different threshold is needed to define LVA and scar tissue.

3) Influences of cycle length variation and direction of wavefront activation during substrate mapping have previously been shown to produce regional and general variations in voltage and conduction velocities (293).

4) Recording technique factors including electrode size, inter-electrode spacing, catheter orientation and tissue contact (255)

1.5.4 Fibrotic Areas as a therapeutic target. Evidence to date

Randomised studies using ablation techniques targeting atrial substrate in AF patients have yielded inconsistent results. A randomised study involving n=124 AF patients showed significantly greater arrhythmia-free survival in the PVI plus LVZ ablation group compared to those with PVI plus-minus linear ablation after a follow up of 12 ± three months [40/59 (68%) vs 25/59 (42%), respectively, p= 0.003] (294). In n=92 AF patients with fibrotic atrial cardiomyopathy, Schreiber et al. used box isolation of fibrotic zones in addition to PVI which led to an arrhythmia-free survival of 69% at 16 months, with lower success rates

in those with extensive fibrosis (295). However, another study involving n=229 symptomatic non-paroxysmal AF patients randomised to 1) PVI plus LVZ guided ablation with additional complex electrogram ablation vs 2) PVI plus linear ablation showed no difference in clinical outcome (74% vs 71%, respectively $p = 0.325$). Subsequently, a meta-analysis published in 2017 involving six studies (four retrospectives, one prospective and one randomised study) involving n=885 patients, 64% with persistent AF suggest improved arrhythmia-free survival in patients undergoing PVI and LVZ ablation in comparison to those who underwent PVI plus wide empirical ablation, with no difference in the adverse event rates in both groups (296).

The recently published ALICIA trial further highlights the limitation of fibrosis-targeted ablation in patients with AF with contemporary technologies (297). In this randomised controlled trial, n=155 patients, 54% with paroxysmal AF) were randomised to either PVI group or PVI + CMR-guided ablation group. No difference in primary clinical outcomes of recurrent arrhythmia at the end of 12 months follow-up. However, the limitations of a low fibrosis burden in patients enrolled in this study, with mean atrial fibrosis of 12%, with only 50% of patients having non-pulmonary vein fibrosis and more than half of the patients with paroxysmal AF might limit the generalization of the findings of this study to patients with persistent AF or with higher degrees of fibrosis burden. Further randomised studies targeting substrate in a group of patients with persistent AF or with higher degrees of atrial fibrosis will be needed to answer this question. Despite this limitation, it also has to be pointed out that in this study, 27% of patients in both groups had a recurrence of AF within 12 months, which highlights the limitation of the current strategy of PVI, even with substrate modification as the ablation strategy in patients with paroxysmal or persistent AF (297).

The equivocal results observed by the ALICIA trial suggest that there may be more than just the presence of fibrosis that influences AF fibrillatory dynamics. Recent evidence suggests additional influences by the type of fibrotic cells and the pattern of fibrosis that determines fibrillatory dynamics. For instance, high-density epicardial mapping performed in patients with acutely induced AF, paroxysmal AF and persistent

AF undergoing cardiac surgery showed complex fractionation in unipolar AF electrograms and higher fractionation index in persistent AF patients, when compared to both paroxysmal and acutely-induced AF patients (298). This corresponded histologically with a higher burden of endomysial fibrosis (fibrotic depositions within cardiomyocytes) on RAA biopsies, but no significant differences were observed in the total amount of fibrosis between all three groups. Additionally, lateralization of CX43 (a gap junction protein between cardiac myocytes) on RAA biopsy samples was also observed in persistent AF patients, compared to paroxysmal and acutely induced AF patients (298). Interestingly, another study utilizing computational models of three different LA models of fibrosis (predominant fibroblasts versus myofibroblasts versus fibrocytes) showed that the fibrocyte LA model resulted in significantly chaotic AF wavefronts propagation, when compared to that of fibroblasts and myofibroblasts (233).

Characterisation of AF through their electro phenotype.

More recently, a study has shown a possible and essential link between the electrophysiologic mechanisms sustaining cardiac fibrillation, the two dominant hypotheses being 1) the presence of multiple wavelets, in which cardiac fibrillation is driven by multiple randomly propagating activating wavefronts (63) or 2) the presence of stable rotational drivers, known as rotors, (299) with the pattern of the underlying cardiac fibrosis. Ng et al. proposed a spectrum of fibrillation electrophenotype (Figure 2), which is intrinsically related to the underlying myocardial substrate; with areas of patchy fibrosis sustaining stable rotational activities, diffuse fibrosis leading to transient or meandering rotational activities and compact fibrosis leading to unstable circuits or multiple wavelets (300). This is based on a recent mechanistic study published by Handa et al. utilizing optical mapping in n=65 Langendorff-perfused rat hearts to investigate the association of ventricular fibrillation (VF) dynamics with underlying tissue fibrosis. (301) In this study, gap junctions were observed to be essential for the electrical cell to cell connectivity and were modulated using rotigaptide to enhance GJ coupling and carbenoxolone for GJ uncoupling. Enhanced GJ coupling stabilized rotational activities (RA) to specific areas in VF rat heart

models in a concentration-dependent manner while decoupling of GJ resulted in infrequent, short-lived RA. In addition, the stability of RA was also influenced by underlying histology patterns analysed by LGE-CMR, with highest number of stable RAs in ventricular myocardium with patchy fibrosis, followed by diffuse fibrosis in which transient and meandering RAs are observed and infrequent stable RAs seen in rat hearts with compact fibrosis. Although this study gives an insight into the link between patterns of fibrillatory dynamics with its underlying substrate, future studies are needed to investigate whether this also applies to patients with AF. Importantly, this study also shows that while the presence and extent of LA fibrosis might be important to prognosticate which patients will do poorly post-AF ablation, the pattern of LA fibrosis might be important to guide ablation strategy in AF patients.

1.6 Electrical remodelling in AF

Electrical remodelling in AF refers to electrophysiological changes that occur on the cellular level that leads to changes in the atrial conduction velocity (CV), atrial refractory period (AERP) and sinus node functional changes. Changes in the electrophysiological properties were initially observed in goat models, where artificially maintained AF models showed a progressive decrease in AERP as AF was sustained for a longer duration (89). In tachy-paced induced AF involving canine models, similar observations were made, involving a significant reduction in AERP along with an increase in LA size (91). Human studies also revealed a shorter AERP in both cohorts of paroxysmal and persistent AF patients, and in AF patients who have had recent cardioversion to sinus rhythm (302, 303). Changes to atrial CV occur progressively over a longer time course compared to changes in the AERP. In atrial tachy-paced canine models, maximal reduction in CV occurred at 42 days, in comparison with one week for a reduction in atrial ERP (304). Shorter durations of induced AF of less than one week have not been observed to make any significant changes to CV (305). A similar reduction in atrial CV has also been observed in persistent AF patients with recent cardioversion. Interestingly, this study also showed no change in conduction times four days post cardioversion despite a recovery of atrial refractoriness (306). In addition, changes to the function of the sinus node have also

been observed in animal and human AF models. In tachy-paced induced AF in canine models, corrected sinus node recovery time remains prolonged up to six weeks post cardioversion compared to baseline (307) while in human AF patients undergoing cardioversion, the presence of sinus node dysfunction was present for at least an hour post cardioversion with gradual recovery over 24 hours (308).

Major electrophysiological alterations that occur on a cellular level in AF include a lower expression of L-type Ca2+ current (ICaL, carried by L-type Ca2+ channels [LTCCs]), rectifier background K+ current (IK1) and constitutive acetylcholine-regulated K+ current (IKACh), and abnormal electrical connection between myocardial cells through changes in the expression and distribution of the gap junction connexin hemichannels (108). During AF, the rate of atrial myocyte activation increases, with a resultant increase in influx of Ca^2 intracellularly. An increase in intracellular Ca^2 leads to Ca^2 current inactivation and activation of Ca^{2+} dependent proteases, kinases, phosphatases and transcription factors such as NFAT (nuclear factor of activated T-cells) (309). Consequently, as a cellular compensatory mechanism to avoid intracellular Ca^{2+} overload, action potential duration is shortened. This reduction of atrial refractoriness, however, leads to an increased tendency to the development and maintenance of AF (309). A reduction of up to 70% of Ca^{2+} current density has been observed in human and animal models of AF (310, 311).

1.6.1 Role of gap junction changes in AF electrical remodelling

Inter-cardiomyocyte electrical impulse conduction is maintained by gap junction subunits, connexin 40 and connexin 43. Connexins are transmembrane proteins that form bridges in the gap junctions between cardiomyocytes (312). Earlier animal studies have shown that deletion of the connexin 40 gene was associated with an increase in P wave duration and decreased atrial CV (313). In patients with AF, abnormally increased expression of connexin 43 along with lateralisation and marked heterogeneity of connexin 40 and 43 have been observed (314, 315). Alterations in connexin expression and localisation results in decreased atrial conduction, creating a substrate for re-entry and maintenance of AF (315).

1.6.2 Role of the autonomic nervous system in AF electrical remodelling

Alterations to the autonomic nervous system (ANS) can both be a result of AF and contribute to the perpetuation of AF. Evidence of alterations to ANS has been seen in canine models of AF, where an increased density and heterogeneity of sympathetic nerve endings have been observed using positron emission tomography in pacing-induced AF models (316). Similar observations were made in human AF patients undergoing cardiac surgery in which right atrial appendage biopsy specimens showed significantly increased sympathetic innervation detected on tyrosine hydroxylase staining compared to controls (317). From a physiological perspective, an increase in adrenergic activation results in intracellular Ca^{2+} overload through phosphorylation by protein kinase A and CaMKII. This results in increased delayed afterdepolarization (DAD), subsequently leading to increased ectopic activity formation via various pathways (318, 319).

1.6.3 Role of microRNAs in AF electrical remodelling

There is increasing evidence suggesting the role of microRNAs in the regulation of gene expression in cardiac electrophysiology, which could contribute to the development of electrical and structural remodelling in AF (108). For instance, downregulation of MIR-1 upregulates I_{K1} in AF, while upregulation of MIR-I in heart failure has been suggested to lead to Ca^{2+}-dependent arrhythmic activity in that group of patients (320, 321). Upregulation of MIR-21 in rat models with post-infarction heart failure has been shown to promote fibrotic remodelling and subsequently, increased tendency to AF development (322). Expression of MIR-328 is elevated three-fold in AF in patients with rheumatic heart disease and results in downregulation of L-type Ca^{2+} channel genes CACNA1C and CACNB1, contributing to adverse atrial electrical remodelling (323).

1.6.4 Role of Inflammation in AF both electrical and structural remodelling

The presence of inflammation has been shown to contribute to both electrical and structural remodelling. By means of histological evidence, the presence of inflammatory infiltrates on endomyocardial biopsies of patients with AF undergoing cardiac surgery has been compared to controls (223). Using blood biomarkers, elevated C reactive protein (CRP), an acute phase protein reactant, has also been observed in patients with AF, with a dose-dependent relationship between CRP levels and AF risk (324, 325). In a clinical setting, elevated CRP is a useful predictor of the recurrence of AF after catheter ablation, cardioversion and in the prediction of post-cardiac surgery AF (326-328). From a pathophysiological standpoint, in terms of electrical remodelling, alterations in the distribution and density of atrial connexin 40 and connexin 43 have been previously associated with inflammation (329). NF-Kb, a protein transcription factor responsible for the regulation of innate immunity, has also been shown to change the expression of cellular sodium channels, which are crucial in generating current for intercellular conduction (330). In terms of structural remodelling, the presence of multiple inflammatory mediators in AF including TGFβ1, TNF-α and Galectin-3 have all been implicated to lead to atrial fibrosis through different pathways (331-333). Interleukins are a group of cytokines which participate in inflammatory response. In context of AF, IL-2 has been shown to shorten action potential duration, while elevated levels have been shown to predict the risk of AF post cardiac bypass surgery and post cardioversion (334-336). IL-6 is a pro-inflammatory cytokine which leads to CRP and TNF-α production, both of which has been associated with increase susceptibility to AF (311). Elevated IL-6 levels itself has been shown to be associated with both increased incidence of AF and AF in setting of postoperative cardiac bypass surgical patients (337, 338).

1.7 Clinical risk factors for atrial fibrillation

Multiple clinical risk factors have been identified that predispose to AF. These can be broadly categorised into non-modifiable (age, sex, genetic predisposition) and modifiable (hypertension, obesity, diabetes mellitus, vascular disease, structural heart disease, heart failure, obesity, alcohol, smoking) risk factors. This will be discussed below:

1.7.1 Age

The relationship between aging and atrial fibrillation is well described in the literature. In the Framingham study which followed n=4731 patients up for 22 years, the prevalence of AF was noted to increase with advancing age, and not surprisingly, age was an independent risk factor for the occurrence of AF (339). In those above the age of 80, the prevalence of AF was estimated to be around 10 to 17% (340). Another epidemiological study showed that the risk of developing AF doubles with each progressive decade of life, exceeding 20% above the age of 80 (341). Underlying mechanisms for this observation include aging-related cardiac electrical changes, diastolic dysfunction with abnormal left ventricular relaxation and increased arterial stiffness in addition to many other comorbidities discussed below that contribute to AF (342, 343). This represents a significant healthcare burden with the increasingly ageing population, while management of these patients in terms of anticoagulation for AF could are also difficult as intracerebral and gastrointestinal bleeding rates in this group are much higher than in the younger cohort (344, 345). Importantly, in elderly patients, AF has also been identified as an independent predictor for the occurrence of ischemic strokes (346).

1.7.2 Sex

Past studies have shown that men are more susceptible to AF than women (347). However, the cumulative risk of developing AF in both genders is estimated to be around 30%, since women live longer than men (348). Additionally, women on average develop AF 10 years after men (348). These differences can be explained through the risk factor profiles, genetic, structural, and electrical differences. There have been observed different interactions between risk factor profiles in both groups that predispose to AF; higher body mass index (associated with higher risk of AF in men than women) and higher total cholesterol is inversely associated with lower AF incidence in women than men (348). Structurally, women in general have a lower LV wall thickness and smaller LA compared to men which might predispose to a lower

incidence of AF (349, 350). In a sub study of patients referred for CMR before AF ablation procedures, interestingly female patients have also shown more atrial fibrosis compared to male patients. However, it is unclear how this results in a lower incidence of AF in women (258). Electrically, studies from animal models have suggested a longer PV potential duration in the PV and LA body in female rabbits compared to their male counterparts, with a more negative resting membrane potential in female PV tissue (351). Importantly, hormonal differences in both genders, including lower testosterone levels in males (352) and increased incidence of AF have been observed in women corresponding to the luteal phase of the menstrual cycle compared to the follicular phase (353). However, AF-related complications including persistent symptoms, stroke and mortality are higher in women, with a previous study also showing that women derive more benefit from anticoagulation than men (354).

1.7.3 Hypertension

Hypertension is linked to an increased risk of developing AF. Data from the Framingham Heart Study showed hypertension to be an independent predictor of AF occurrence (339). Additionally, poor blood pressure control in hypertensive patients on medications was also associated with an increased risk of AF (355). On a mechanistic level, the relationship of hypertension with AF can be explained through hypertension-induced dysregulation of the renin-angiotensin-aldosterone system resulting in atrial electrical and structural remodelling. High levels of angiotensin 2 have previously been observed in hypertensive patients (356), while angiotensin 2 has been shown to cause changes to cardiac electrical conduction and is pro-inflammatory (357). Similarly, higher aldosterone levels have also been shown to be pro-fibrotic and negatively affect myocardial ion channel function and distribution (358). Direct effects of hypertension on electrical and structural remodelling which favours AF have been shown in animal models, where a greater mean atrial ERP, LA dysfunction, conduction slowing and interstitial fibrosis have been observed in hypertensive models, while in human studies, hypertensive patients had a lower conduction velocity, with a larger low voltage area compared to controls (180, 359).

1.7.4 Diabetes

Multiple epidemiologic studies have suggested a potential link between diabetes mellitus and AF. For instance, the ARIC study (Atherosclerosis Risk in Communities) study which involved n=15792 African American and Caucasian patients aged between 45-64 years showed an independent association between type 2 diabetes mellitus (T2DM) and AF with a hazard ratio of 1.35 (95% CI 1.14-1.6) after adjusting for known cardiovascular risk factors.

Mechanistically, diabetes mellitus has been linked with several adverse atrial structural and electrical remodelling that favours the development of AF. Structurally, interstitial fibrosis has been observed in both animal and human models of DM. Specifically, histological analysis from cardiac biopsy involving diabetic patients showed increased cardiac fibroblasts, and increased expression of Type 1 collagen. This is thought to be secondary to an increased production of angiotensin 2, reactive oxygen species production and enhanced TGF-Beta signalling in setting of hyperglycemia, all of which contributes to collagen synthesis and fibrotic depositions. The presence of fibrosis is crucial to non-uniform electrical conduction slowing in the atria, wavefront fragmentation and subsequently, formation of electrical re-entry which favours AF initiation. Electrically, a prolonged atrial action potential duration has been observed in animal diabetic models. This has been attributed to a reduction of sodium current (which affects the atrial action potential upstroke velocity and hence, conduction slowing) with an associated reduction in acetylcholine-activated potassium current. In addition, some studies have observed the potential effect of diabetes mellitus on the spatial distribution of gap junctions which plays an essential role in cell-to-cell electrical conduction. Finally, the presence of autonomic dysfunction, measured using heart rate variability, has also been shown to be a predictor of AF development in diabetic patients, independent of other known cardiovascular risk factors.

1.7.5 Obstructive sleep apnea

There is an increasing body of evidence suggesting a link between obstructive sleep apnea (OSA) and the incidence of AF. Epidemiological studies have shown the prevalence of OSA to be significantly higher in AF patients than non-AF patients, present in up to 3 out of 4 patients with AF (45, 360, 361). Additionally, the presence of OSA in AF patients has also been associated with poor clinical outcomes, including a lower response rate to antiarrhythmic therapy (46) and cardioversion (360) and also a higher AF recurrence post-AF catheter ablation procedures (362). From a mechanistic perspective, the presence of OSA has been associated with repeated episodes of hypoxia and hypercapnia which leads to higher activation of the sympathetic nervous system (363), higher levels of inflammation (364), atrial structural and electrical remodelling including shortening of atrial effective refractory periods (365), longer sinus node recovery time (366) and presence of atrial low voltage areas, suggestive of fibrosis (366), and autonomic nervous system dysregulation (367). Additionally, the presence of OSA is usually associated with the presence of other comorbidities that contribute to AF including hypertension and obesity. The gold standard of treatment for OSA is the use of continuous positive airway pressure (CPAP). Previous studies have shown the efficacy of CPAP therapy in AF patients with OSA in reverse structural and electrical remodelling of atria (368, 369) which led to an improvement in clinical outcomes including response to cardioversion (360) and improved freedom from AF recurrence post AF catheter ablation (370, 371).

1.7.6 Obesity

Links between obesity and the development of AF have been observed in multiple epidemiological studies. For example, long-term follow-up data of >10 years from the Framingham Heart Study showed obesity to be predictive of AF. Another study also showed an independent association between obesity and AF, regardless of the diagnosis of obstructive sleep apnea. The ARIC study showed that 20% of every AF patient can be linked to underlying obesity (372) while another study showed that every 5-unit increment in body mass index (BMI) can be linked to up to 29% risk of developing AF, with also a higher risk of both postoperative AF and post-ablation AF recurrence (373). Multiple underlying mechanisms

have been implicated in this association. These include: 1) increased LA size, LA stretch and reduced LA emptying in obese patients (374) 2) the presence of hypertension as a comorbid disorder, both of which co-exist frequently (375) 3) a larger volume of epicardial and pericardial fat in obese patients, which are pro-inflammatory (376) 4) underlying atrial electrical remodelling has been observed in obese patients including conduction slowing and increased conduction heterogeneity (377) 5) underlying cardiac structural changes including the presence of inflammatory infiltrates, lipidosis, and LA fibrosis (377, 378). Not surprisingly, studies targeting a lower weight in AF patients have resulted in a lower AF burden in this cohort. Pathak et al showed in the LEGACY study that AF patients with significant intentional weight loss of >10% over 5 years follow-up had a - sixfold higher likelihood of achieving arrhythmia free survival (379). Structured weight management programs in dedicated AF clinics have similarly shown clinical benefits with a reduction in AF burden and a reduction in the risk of AF recurrence (380).

1.7.7 Congestive heart failure

Electrical and structural remodelling in human models of heart failure

In canine models of AF and heart failure, a reduction of ejection fraction on serial echocardiogram was associated with a significant progressive increase in biatrial volumes and degree of atrial fibrosis (381). In n=21 AF patients with congestive heart failure with a mean LV ejection fraction of 25%, Sanders et al observed an increase in atrial ERP, an increase in atrial conduction time, prolonged corrected sinus node recovery time and an increased number of double potentials along the crista terminalis, when compared to age-matched controls (290). Using optical voltage-mapping in human coronary-perfused ventricular free wall preparations, Federov et al also observed a significantly longer atrial action potential duration and functional refractory period in failing hearts, compared to non-failing hearts (382). Using complex fractionated electrograms (CFAE) as a surrogate marker for electrical complexity, a more recent prospective study involving n=60 persistent AF patients analysed atrial differences in CFAEs between

patients with heart failure (n=30) and in patients without heart failure (n=30). Haldar et al observed significantly higher regions of CFAEs in patients without heart failure, than in patients with heart failure. A stepwise approach with PVI followed by linear lesions and CFAE ablation was performed sequentially if AF persisted after each strategy. Interestingly, this strategy was associated with a more significant reduction in lower total biatrial CFAE areas post-ablation in the heart failure cohort, which translated to a greater freedom from atrial tachyarrhythmia, compared to the non-heart failure cohort(383).

Structurally, increased amounts of fibrotic tissue, measured using CMR-LGE have been observed in AF patients with LV systolic dysfunction (384). Analysis of the atrial extracellular matrix of AF patients with congestive heart failure has revealed downregulation of the protein level of tissue inhibitor of metalloproteinase (TIMP-2) and upregulation of matrix metalloproteinase (MMP-2), when compared to control (385). When LA structure and function were compared between patients with HFrEF and HFpEF, Melenovsky et al observed significantly larger LA volumes in HFrEF patients, while significantly higher LA peak pressures, stiffer LA, and higher stress wall variations with higher AF burden were observed in patients with HFpEF (386). A more recently published meta-analysis involving 61 studies investigating the differences in left atrial structure and function between HFrEF (n=8806) and HFpEF (n=9928) patients showed similar LA volumes and LV filling pressures in both groups, but a significantly lower LA reservoir strain in HFrEF patients and a significantly higher AF burden in HFpEF AF patients (387).

Clinical studies have suggested a potential benefit of restoration of sinus rhythm via medical therapy in AF patients with both heart failure with preserved ejection fraction (HFpEf) and heart failure with reduced ejection fraction (HFrEf). In a single-centre observational study involving n=570 paroxysmal and persistent AF patients undergoing PVI cryoablation, freedom from atrial tachyarrhythmia recurrence after 48 months follow-up was significantly lower in the HFpEf group compared to the group without HFpEf (P=0.049). In addition, significant symptomatic improvement, measured using the New York Heart Association (NYHA) classification was observed and accompanied with evidence of LV reverse remodelling, structurally in the

HFpEf group (388). In patients with AF and HFrEf, restoration of sinus rhythm has shown clinical benefit, particularly in AF patients undergoing catheter ablation. In the CASTLE-AF study which randomised n=363 AF patients with LV ejection fraction <35% to catheter ablation or medical therapy, patients who underwent catheter ablation for treatment of AF had a significantly lower cardiovascular death (P=0.008), cardiovascular hospitalisations (P=0.04) and heart failure hospitalisation (P=0.004) compared to the group on medical therapy. In addition, improvement in median LV ejection fraction was also significantly higher in the ablation group compared to the medical therapy group (8% versus 0.2%, P=0.005) (10). However, the clinical benefit of using antiarrhythmic therapy in AF patients with LV systolic dysfunction is less clear. An earlier randomised clinical study by Torp-Pederson et al showed no difference in cardiovascular mortality but a significant reduction in heart failure hospitalisations (hazard ratio 0.75; CI 0.63 – 0.89) in AF patients with LV systolic dysfunction randomised to dofetilide therapy versus placebo. In contrast, Roy et al showed no significant differences between cardiovascular mortality and hospitalisations in n=1376 AF patients with LV systolic dysfunction randomised to a rate versus rhythm control strategy using antiarrhythmic drugs (389). Another smaller single center randomised clinical study involving n=55 AF patients with LVEF < 50% randomised to catheter ablation versus rate control strategy showed significant improvement in LV ejection fraction (P=0.015), peak oxygen consumption (P=0.014) and heart failure symptoms (P=0.001) in the catheter ablation group compared to the rate control group. However, clinical benefits have not been observed in other modalities of sinus rhythm restoration such as using antiarrhythmic therapy. The AATAC trial randomised n=203 persistent AF patients with LV ejection fraction < 40% to catheter ablation versus the amiodarone group. After a median follow-up of 24 months, overall mortality and unplanned hospitalisation rates were significantly lower in the catheter ablation group compared to the medical therapy group (8% versus 18%, P=0.037 and 31% versus 57%, P<0.001, respectively) (390). It is likely the reason for the clinical outcomes observed lies in the inherent superiority of catheter ablation to maintain sinus rhythm compared to antiarrhythmic drug therapy, which also has

been associated with high incidences of side effects and drug discontinuations. For instance, in the CASTLE-AF study, 63% of patients who were randomised to catheter ablation remained in sinus rhythm after 60 months follow-up compared to 22% in the medical therapy group (10).

Mechanistically, similarities exist between the pathophysiologic sequences for the development of AF and heart failure. Activation of the renin-angiotensin-aldosterone system (RAAS) and neurohormonal imbalances underlie the development of heart failure. Similar changes are also observed in AF, where excessive activation of RAAS leads to atrial stretch and atrial fibrosis, consequently non-uniform electrical propagation, and electrical re-entry (391-394). In addition, abnormalities in calcium handling seen in heart failure patients have also been observed in AF patients, as this could lead to delayed after-depolarisation and arrhythmogenesis (395). Tachycardia-induced cardiomyopathy is another recognised clinical complication of AF. Rapid ventricular contractions secondary to AF have been shown to result in LV dysfunction (396). In animal models, chronic tachycardia has been shown to result in increased oxidative stress (397), reduced myocardial oxygen storage (398), cardiomyocyte loss (399)and reduced beta-adrenergic responsiveness (400). Further, irregular rapid atrial contractions could result in a reduction in cardiac output by a reduction in LV filling especially in the presence of diastolic dysfunction (396).

Importantly, the presence of LV systolic dysfunction has been linked with poorer clinical outcomes following catheter ablation for AF. In a prospective cohort study involving highly symptomatic AF patients, Cha et al compared three of highly symptomatic AF groups 1) n=157 patients with diastolic dysfunction and preserved LV systolic function 2) n=111 patients with LV systolic dysfunction (LV ejection fraction ≤ 40%) and 3) n=100 patients with normal LV systolic and diastolic function. They observed an increased relative risk of arrhythmia recurrence in patients with LV systolic dysfunction (HR 1.8, 95% CI 1.1 to 3.1, P=0.02), and slightly lower in patients with diastolic dysfunction (HR 1.7, 95% CI 1.0 to 2.7, P=0.04) when compared to patients with normal LV systolic and diastolic function (401). On the contrary, another retrospective study by Black-Maier et al involving n=230 AF patients who underwent catheter ablation

(n=133 patients with HFpEF and n=97 patients with LV systolic dysfunction (defined as LV ejection fraction of <50%)), freedom from recurrent atrial tachyarrhythmias was similar in both HFrEF and HFpEF patients (33.9% versus 32.6%, HR 1.47, 95% CI 0.72-3.01) (402). However, this difference observed may be likely due to differences in baseline demographics of patients in both these studies; patients included in the study by Black-Maier et al were older, with a higher incidence of hypertension and diabetes mellitus (402). However, there has been limited evidence to date, exploring the association between abnormal LV GLS with clinical outcomes post catheter ablation. A prospective study involving n=135 AF patients undergoing catheter ablation showed that LV GLS was an independent predictor of AF recurrence post-ablation (HR 1.13, 95% CI 1.03-1.24, P<0.01), even after adjusting for traditional AF clinical risk factors and LA size and functional parameters (403).

1.7.8 Smoking and alcohol

Epidemiological studies have suggested a strong association between smoking and AF. This risk is higher in current smokers than former smokers, with a positive dose-dependent relationship observed between tobacco use and risk of incident AF (404, 405). In addition, the risk of developing AF is also significantly higher in passive smokers and in patients exposed to tobacco use during the gestational period or early childhood (406, 407). Mechanistically, it is thought that smoking increases the risk of myocardial ischemia by reducing myocardial oxygen demand, and myocardial work and promotes inflammation, thrombosis and oxidative stress (408, 409). Consequently, this predisposes to incident AF through the development of atrial ischemia, heart failure and myocardial infarction. In canine models exposed to nicotine, an increase in myocardial interstitial fibrosis has been observed, attributed to the downregulation of atrial microRNAs miR-133 and miR-590, and subsequent increase in transformin growth factors β1 and β2 which is profibrotic (410). Electrically, nicotine exposure also prolongs action potential duration, through the blockade of inward rectifier potassium channels and a reduction in transient outward potassium current, which contributes to arrhythmogenesis (411, 412).

Alcohol consumption has also been linked to the incidence and burden of AF. One meta-analysis of seven prospective studies has shown that even one standard drink of alcohol per day increases the relative risk of AF by 1.08 (413). Complete abstinence from alcohol has also been shown to be associated with a lower risk of AF recurrence compared to light alcohol drinkers in a recent randomised study of n=140 AF patients (414). Another study has also shown that low levels of alcohol intake increase the risk of AF in a community-based cohort of 107845 patients. The mechanisms behind this in this study were postulated to be secondary to myocardial stress and injury, as reflected by a rise in NT-proBNP levels and hsTnI levels (415). Additionally, from a mechanistic perspective, other studies have shown that alcohol exhibits a direct toxic effect on the myocardium, potentially leading to alcoholic cardiomyopathy (416) and could also indirectly contribute to AF via activation of pro-inflammatory pathways (416).

1.7.9 Limitations to the use of antiarrhythmic therapy

1.7.9.1 High Incidence of adverse events

A major limitation to the long-term use of antiarrhythmic therapy is the high incidence of adverse events. In the AFFIRM study which randomised n=4060 AF patients to different antiarrhythmic therapies, the rate of discontinuation of antiarrhythmic therapies was 21% after one year; highest in the flecainide group, 39% and lowest in the amiodarone group, 13% (417). Earlier studies have observed varying degrees of adverse events from antiarrhythmic use. CTAF study which was a prospective study that included n=403 AF patients observed adverse events requiring discontinuation as high as 18% in patients taking amiodarone compared to 11% in patients on sotalol or propafenone (26). Similarly, Bellandi et al observed discontinuation of antiarrhythmic therapy of approximately 10% due to sotalol and 9% due to propafenone (418). Results from a recent posthoc analysis of the RACE 3 study showed adverse events requiring discontinuation in approximately 13% of the cohort, highest in the dronedarone group (33%), followed by sotalol (22%), amiodarone (7%) and flecainide (5%) (419).

1.7.9.2 Low overall efficacy rates for conversion to sinus rhythm

Further, antiarrhythmic use has also been associated with a poor overall efficacy rate in maintaining sinus rhythm. In general, amiodarone has been observed to be more effective when compared to other antiarrhythmics. CTAF study which included n=403 AF patients followed up for 16 months showed the highest success rates with amiodarone use, with 65% of patients without AF recurrence followed by both sotalol, 37% and propafenone, 37% (389). In a double-blind, randomised trial involving n=665 persistent AF patients randomised to amiodarone versus sotalol, spontaneous cardioversion to sinus rhythm were similar in both group and occurred in 27.1% of patients on amiodarone versus 24.2% of patients on sotalol therapy. However, the median time to AF recurrence was significantly longer in patients on amiodarone (809 days), compared to patients on sotalol (209 days), P<0.001 (25). Another randomised study involving n=1182 persistent AF patients who underwent cardioversion and subsequently commenced on antiarrhythmic therapy, AF recurrence rates were 83% in the placebo group, 67% in patients on sotalol and 65% in patients on quinidine and verapamil (420). When amiodarone was compared to dronedarone, AF recurrence was significantly higher in the dronedarone group compared to amiodarone (75.1% versus 58.5%, P<0.0001) after 12 months, with no significant differences observed with regards to adverse events requiring drug discontinuation (P=0.129) (421).

1.8 Electroanatomic mapping, phase mapping and other quantitative methods for fibrillatory dynamics in Atrial Fibrillation

1.8.1 Principles of Electroanatomic Mapping and Clinical Utilisation

Electroanatomic mapping (EAM) has been increasingly used as a modality for the diagnosis and treatment of cardiac arrythmias. These systems utilise an electromagnetic or impedance-based method to create a precise 3D anatomical map of a patient's cardiac chamber (422). Briefly, intracardiac electrograms are collected by a mapping catheter, and the activation times are then compared to a preselected electrogram

reference (422). The collected points are assigned to isochronal colours depending on their timing of activation which allows the creation of activation maps. In addition, voltage maps can be created by the system by analysis of the collected intracardiac signals amplitude, which allows the assessment of low voltage areas or scar regions in the heart that may be serve substrate for certain arrythmias (422). In addition to defining cardiac chamber anatomy, EAM allows real time assessment of intracardiac catheter location through non fluoroscopic methods, which could reduce radiation exposure, delineates arrythmia mechanisms (focal versus reentrant) in combination with other mapping methods such as entrainment mapping and allows integration of the EAM with other non-invasive imaging modalities such as MRI or CT (422).

Two commonly used EAM include the EnSite Velocity (Abbott), and CARTO (Biosense Webster, Diamond Bar, CA, USA) (423). The CARTO mapping system utilises a low magnetic field emitter placed under the operating table and a magnetic sensor at the tip of the mapping catheter. The change in strength and direction of the mapping catheter in relation to the magnetic patch is used to create the electroanatomic maps (423). In contrast, the EnSite Velocity system is an impedance-based system which utilises three pairs of patches placed on the thorax to produce a transthoracic orthogonal electric field surrounding the heart (423).

HD grid mapping catheter

In RENEWAL-AF, the Ensite Velocity (Abbott) EAM system along with the Advisor HD grid mapping catheter was primarily used for intracardiac electrogram collection for the clinical studies. The Advisor HD grid has 18 electrodes, arranged in four parallel splines in a 4 by 4 electrode configuration pattern (424). Each electrode is 1 mm in size and are spaced 3 mm apart (424). There are two further electrodes on the proximal end of the mapping catheter. The multiple electrodes arranged with small interelectrode spacing arranged in an orthogonal orientation allows rapid collection of multiple intracardiac electrograms at any

given time (424). Integration of the intracardiac signals into the Ensite Velocity system then allows signal annotations via proprietary algorithms where the maximum rate of voltage change (dv/dt) on unipolar electrograms, or maximum amplitude of bipolar electrograms are annotated to create either an activation map (via comparison to an intracardiac signal reference) or voltage map (absolute intracardiac amplitude) (424).

Figure 1.2: Example of HD grid mapping in AF ablation

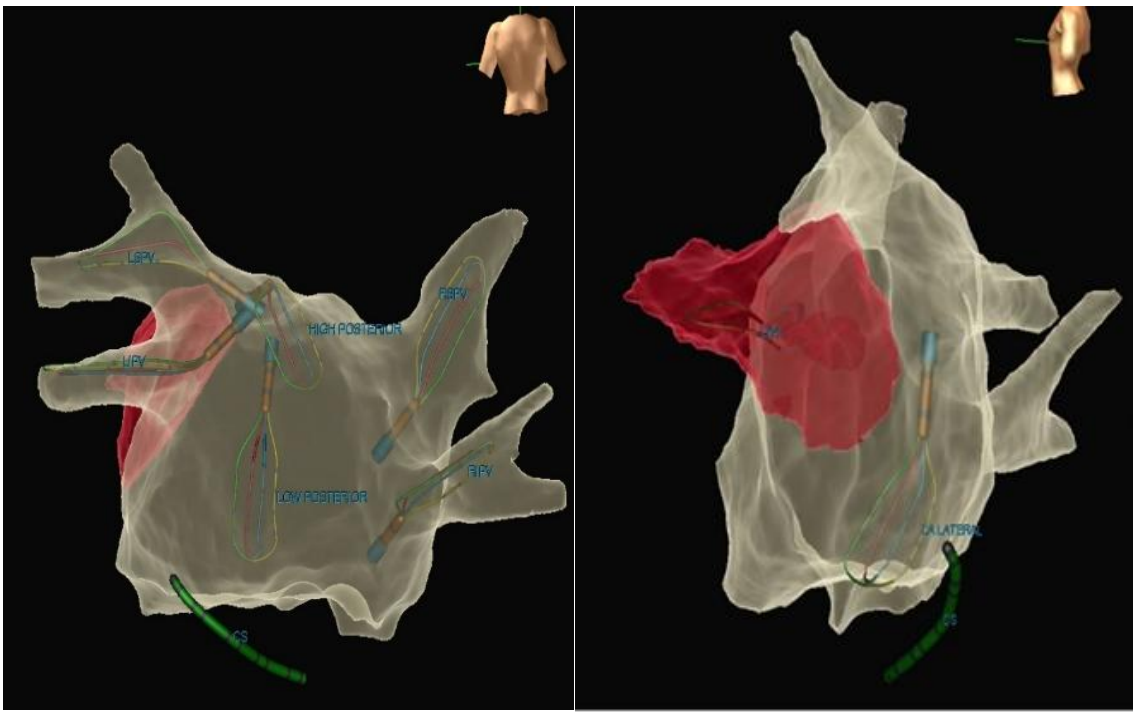
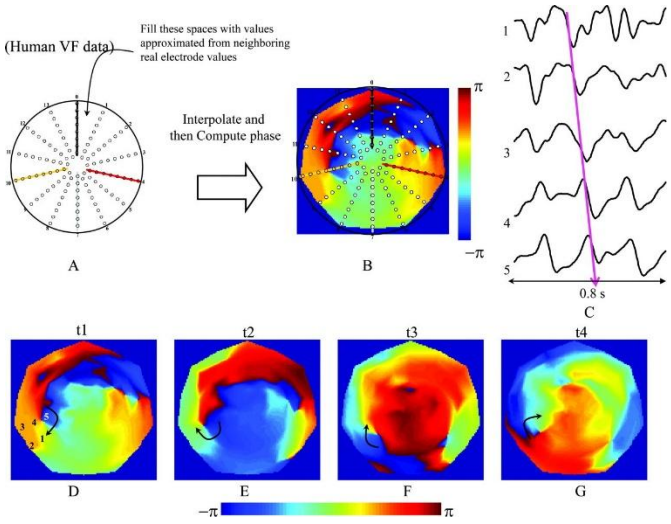


Figure 1.2 showing on the left: PA view of the LA. Red tag applied for the LAA. Sequential sampling was performed for all the four pulmonary veins and extra pulmonary structures including the posterior wall and the LAA. On the right is a left lateral view of the LA. Position of coronary sinus catheter tagged in green and views of the HD Grid catheter in relation to the thorax on the upper right side.

1.8.2 Phase mapping

During fibrillation, the progression of the action potential through different regions of the cardiac myocardium can be tracked using phase mapping. Phase maps are created using optical or electrical mapping on the endocardium or epicardium of the heart. Phase mapping computes a signal's relative timing (i.e., phase) over its entire duration and does not depend on the amplitude of an electrogram, as this is prone to contamination by artifacts/noise. Rather, the spatiotemporal characteristics of a signals phase map are determined by calculating the instantaneous phase of all electrograms acquired over a region of endocardium or epicardium, plotted over time (425) (Figure 1.2).

Figure 1.3: Phase map of human VF with electrodes embedded.

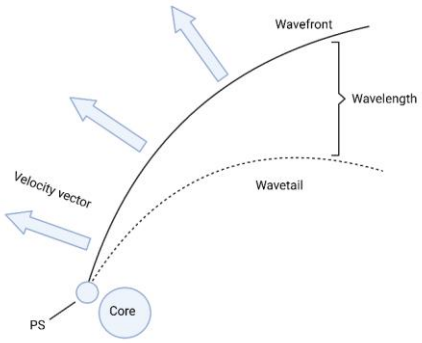


In panels A and B, 2D phase map of human VF, was recorded using multiple electrodes. In panel C, electrogram recordings along the path of the rotating phase over time. In Panels D to G, showing the progression of movement of the rotating phase pattern over time. Adapted from Umapathy et al (425)

Mathematically, the method of computing the instantaneous phase of a signal is typically achieved through the calculation of the Hilbert transform. In the context of fibrillation, this allows the relative

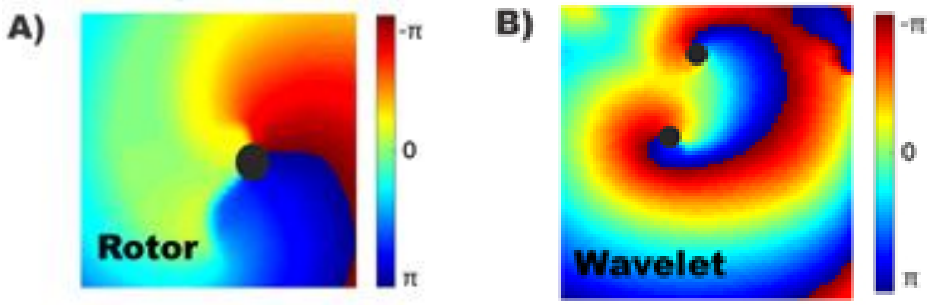
timing of electrical activity with respect to the action potential cycle to be visualized. This -is typically done using a colour-coded heat map (also known as a phase map), which for example will plot from red (denoting earliest activation timing) to blue (denoting latest activation timing), therefore visualising the sequence of activation of a region of myocardium at a particular time (Figure 1.3 and 1.4). It can be noted that the completion of one action potential cycle is thus represented by the full progression from -π to π (i.e., from red to blue). An important feature of the phase map is the pivot point where all the values of phase from -π to π (i.e., from red to blue) hinge upon, which represents a topological defect where there is indeterminate phase. This feature is also known as a phase singularity (PS) point, physiologically relating to areas of tissue where the core comprises of unexcited but excitable tissue. Using these PS points, a rotor is typically defined as a PS which has completed two full progressions from -π to π around its core (425).

Figure 1.4: Schematic of phase singularity



Wavefront and wave tail originate and meet at a central core, known as the phase singularity. Conduction velocity is the slowest at the region of highest wavelength curvature, near the central core. Adapted from Guttler et al (426)

Figure 1.5: Phase singularity detected on phase mapping.



A: Phase singularities at the pivot site of rotors. B: Phase singularities detected at the free ends of wavelets. Red areas denote region of earliest activation, and blue areas denote the region of the latest activation. Adapted from Dharmaprani et al (16). Used with permission from Wolters Kluwer Health.

The use of phase maps in cardiac fibrillation has significantly enhanced our understanding with regard to the behaviour of fibrillatory waves in human cardiac fibrillation. For instance, using epicardial sock mapping of VF in n=10 patients undergoing cardiac surgery, Nash et al showed preponderance and meandering of PS around regions of anatomic heterogeneities, and also a predilection of PS around cardiac regions with wave breaks (427). In AF, another study has shown the anchoring of PS to atrial locations with high action potential duration (APD) gradient, specifically around the junction of the inferior pulmonary veins to the LA and the central anterior LA, in the absence of fibrosis. However, in the presence of fibrosis, a clustering of PS was observed in and around the borders of the fibrotic regions (236). In addition, other groups have suggested that stable PS behaves as a "driver" for AF and hence, may be a suitable target for ablation in AF (428, 429). However, the clinical utility of this approach has yet to be proven (430). Limitations of phase mapping include the potential false detection of PS, specifically in settings with poor spatial resolution, poor endocardial contact of the mapping catheter, and the presence of far field signals and local noise (431-433).

1.8.3 Dominant frequency

A characteristic feature of electrograms during fibrillation is complex and disorganised signals in the time domain, with constantly changing amplitudes and the lack of a clearly identifiable cycle length (434). As such, analysing useful features from these signals in the time domain can be quite difficult. Dominant frequency (DF) analysis can help provide insights into these complex fibrillatory signals by instead transforming electrograms into the frequency domain, allowing electrograms to be characterised into its constituent frequencies. This is done by calculating the power spectrum of the signal, with the frequency corresponding to the highest power considered to be the dominant frequency of the signal. It has been hypothesised that areas of high DF represent areas or rotors driving fibrillation thought to activate at much higher frequencies, thus targeted ablation to these areas thought to terminate AF (434).

Earlier studies in DF have suggested that the highest DF values correspond to the core of mother rotors in simulation studies, while in human studies, a higher DF has been shown to be in the PV and LA, compared to the RA suggesting a gradient of reduced fibrillation complexity from the LA to the RA (191, 435, 436). Lower global DF on based on invasive and non-invasive measurements from surface ECG has also been linked to a better long-term outcome post-catheter ablation in AF patients (437, 438). From a therapeutic perspective, although earlier observational studies have suggested that areas of high DF could potentially be clinically relevant with observed prolongation of AF cycle length or termination of AF while ablating high DF sites (191), a randomised clinical study comparing DF ablation to conventional treatment in patients with early paroxysmal AF has not shown any difference (439). However, the use of DF in clinical practice might be limited by the potential detection of far-field potentials and noise (440, 441). In addition, there have also been concerns raised that high DF sites might actually represent sites of wavefront collisions while the accuracy of DF for detection of driver sites might also be reduced in the presence of significant rotor meandering (438).

1.8.4 Entropy

Shannon entropy (ShEn) is an information-theoretic measure that quantifies information content. From a signal analysis perspective, ShEn provides a measure of the unpredictability or complexity of a given signal. In the context of AF analysis, ShEn has been used to measure the information content of an ECG or EGM and is calculated using histograms of electrogram voltage. Predictable signals (with more consistent/regular amplitudes) such as sinus rhythm on an ECG will have low entropy values as they will associate with more narrow voltage histograms. On the other hand, unpredictable signals (with irregular amplitudes) such as atrial or ventricular fibrillation on ECG will have more varying voltages and therefore produce wider voltage histograms, hence high entropy values (442). In terms of AF therapy, ShEn can be used to localise areas of high and low entropy based on electrogram or optical mapping data, with areas of high entropy potentially correspond to driver regions. In addition, the core of rotors will show higher

ShEn values, given it has more complex fragmented signals with varying amplitudes, while areas further from the core will show lower ShEn value, given activation wavefronts are more regular away from the pivot region. An inverse correlation between ShEn and distance from rotational core has previously been shown in paired optical mapping and bipolar electrogram data in animal models (442). However, contrary to the findings from Ganesan at al, other findings have shown a lower ShEn value at the core of rotational activity (443, 444). Importantly, false positive high ShEn for pivot regions of rotors have also been shown to be a result from complex interactions between wavefront propagation from various directions (445).

1.8.5 Renewal theory: A novel quantitative framework for assessment of fibrillatory dynamics

Renewal theory is a branch of probability theory that seeks to understand and model the probability distributions of statistically independent events. The mathematics of renewal theory is somewhat complex, but the key principles and power of renewal theory can be understood with the help of some relatively simple analogies. A classic example of a renewal process is flipping a fair coin, whose outcome is a head or a tail. If a coil is flipped once, the outcome (head or tail) is uncertain. However, as we flip the coin more times, we would expect that the probability of landing on heads or tails overall would converge towards 50%, despite the outcome of each coin toss remaining almost impossible to predict. Other examples could be rolling a dice or spinning a roulette wheel. On any individual realisation of the system, the outcome is very difficult to predict. However, if each of these systems is observed over many rolls or spins, the long-term probabilities will converge and can be identified with a high degree of accuracy.

The reason long-term probabilities converge in this way can be related to statistical independence. Statistical independence describes the notion whereby the outcome of one event does not influence the outcome of another. For example, given the example of the fair coin, knowing that the outcome of a toss is heads does not necessarily mean we can predict whether the next toss will produce a head or tail. However, this also means that the probability of landing on a head after 1 toss, 10 tosses or 1000 tosses

is mathematically equal, and therefore will result in the same probability of landing on a head over the course of all coin flips, which is also referred to as a constant 'instantaneous hazard rate'.

This same kind of notion, namely that statistically independent events will eventually converge to predictable long-term probabilities, is the basis of renewal theory. In a renewal process, although the timing of individual events is statistically independent, the long-term average rate of events is predictable (446). Specifically, this long-term average rate can be calculated/predicted by evaluating the probability distribution generated from the events.

The simplest type of renewal process is a Poisson process, in which the underlying long-term event rate is constant (Figure 1). A characteristic of this type of renewal process is that interevent times will produce probability distributions with an exponential shape. Mathematically, it can be shown that if the interevent times follow such an exponential distribution, then the underlying data generating process is a Poisson renewal process (446).

The most familiar example of Poisson renewal process is radioactive decay. If we take a lump of a radioactive isotope, the timings of individual atomic decays are statistically independent due to probabilistic quantum tunneling events, but the decay rate converges to a stable rate over time. This produces characteristic exponential decay curves for individual radioisotopes, enabling the decay rate to be determined with great accuracy. This is also the underlying principle used in the construction of atomic clocks, considered to be the most accurate clocks in the world.

The key properties of a Poisson renewal process are summarised as below (Figure 1). These are:

(i) Individual events are statistically independent, i.e., the occurrence of one has no bearing on the probability another event will occur.

(ii) The probability distribution of inter-event times is exponential, i.e., the timings between consecutive events will give probability distributions with an exponential shape.

(iii) The long-term average event rate or instantaneous hazard rate (given by the probability of an event occurring per unit time) is constant.

(iv) The cumulative hazard of events is a straight line, which indicates a constant long-term average rate.

Figure 1.6: Properties of a system displaying Poisson renewal process

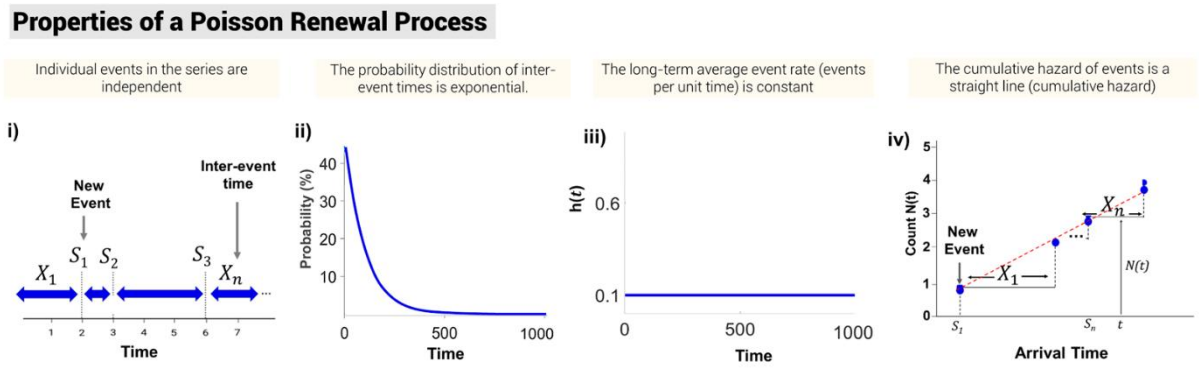


Figure adapted from Dharmaprani et al (16)

1.8.5.1 Mathematical Properties of the Poisson Renewal Processes

The renewal rate constants are calculated using a maximum likelihood-based approach by fitting inter-event times to an exponential distribution using the following equation: -

$$f(t) = \lambda e^{-\lambda t}\ t\ \geq 0$$

where it is time and λ is the PS destruction or formation rate (referred to as λ_d and λ_f, respectively (16))

In the case of inter-formation event times, the probability distribution yields the rate constant λ_f, which in effect is the long-term average formation rate of PS. In the case of PS lifetimes, this probability distribution yields λ_d which is the average rate of destruction of PS. From the above equation, λ_f is derived from fitting

a distribution to inter-event formation times and λ_d from fitting a distribution to PS lifetimes. The close correlation of λ_f/λ_d calculated from event time distributions to that derived directly from PS time series data has been demonstrated (447).

1.8.5.2 Evidence for renewal process in nature

Renewal processes are a common motif in many other natural systems, ranging from radioactive decay to action potential firing in neurons and survival analysis (448, 449). The renewal process and exponential distribution are explained as inevitably arising in natural systems through the actions of multiple uncorrelated microscopic processes(450). The notion of statistically independent particle behaviour leading to predictable probability distributions, known as the molecular chaos theory, underlies the kinetic theory of gases and is the basis of statistical mechanics (451).

1.8.5.3 Rationale for Focusing on phase singularities

The rationale for focusing on PS in AF is that these are located both at the heart of re-entrant circuits and at the free ends of wavelets during fibrillation. Gray et al. identified some key rules regarding PS based on principles of topology: phase lines cannot intersect; PS are joined by other isophasic lines to PS of opposite chirality or non-conducting boundaries; and PS form and terminate as oppositely rotating pairs (452). In our study, we reasoned that because PS are effectively subject to a quasi-stationary rate of decay, an exponential distribution should be observed in both PS overall and the subset of PS that are longer-lasting and have undergone one or multiple rotations (16). In fact, this is what we observed (16). We also noted that groups who have focused on PS arising only from re-entrant circuits that have undergone a complete rotation also find an exponential distribution of PS lifetimes. In effect, this would suggest that PS at the free ends of wavelets and those at the centre of rotors are effectively one class on a biological continuum, rather than being separate classes of re-entrant circuits.

1.8.5.4 Rationale for a Renewal Theory Approach in AF

The defining property that sets apart AF from other arrhythmias is disaggregated, disorganised and turbulent electrical wave propagation in terms of wave propagation in space and time (453, 454). This breakdown in coherence has been conceptualised as a conservative, non-dissipative form of chaos (455, 456). In our study, we reasoned that, given the highly disorganised nature of AF, the formation and destruction of re-entrant circuits in AF could reasonably be considered statistically independent events (16). Our suggested rationale for this proposition is that because of the disorganised nature of AF, where wave propagation is disaggregated, PS that form in one part of the chamber are effectively statistically independent of PS that form in other parts of the atrial chamber. This has recently been evaluated by consideration of the autocorrelation of PS interval series, which shows whether events are occur with correlation, in turn identifying whether the condition of statistical independence is met. Using this approach, we performed thorough systematic evaluation to show that PS can indeed be modelled as statistically independent (457). If the formation and destruction of re-entrant circuits were statistically independent, we reasoned, by analogy with other systems where statistical independence is a key property, that the formation and destruction rates of re-entrant circuits in AF should converge to a constant rate (16). This would be expected to yield, under the principles of renewal theory, an exponential distribution of inter-formation times and re-entrant circuit lifetimes.

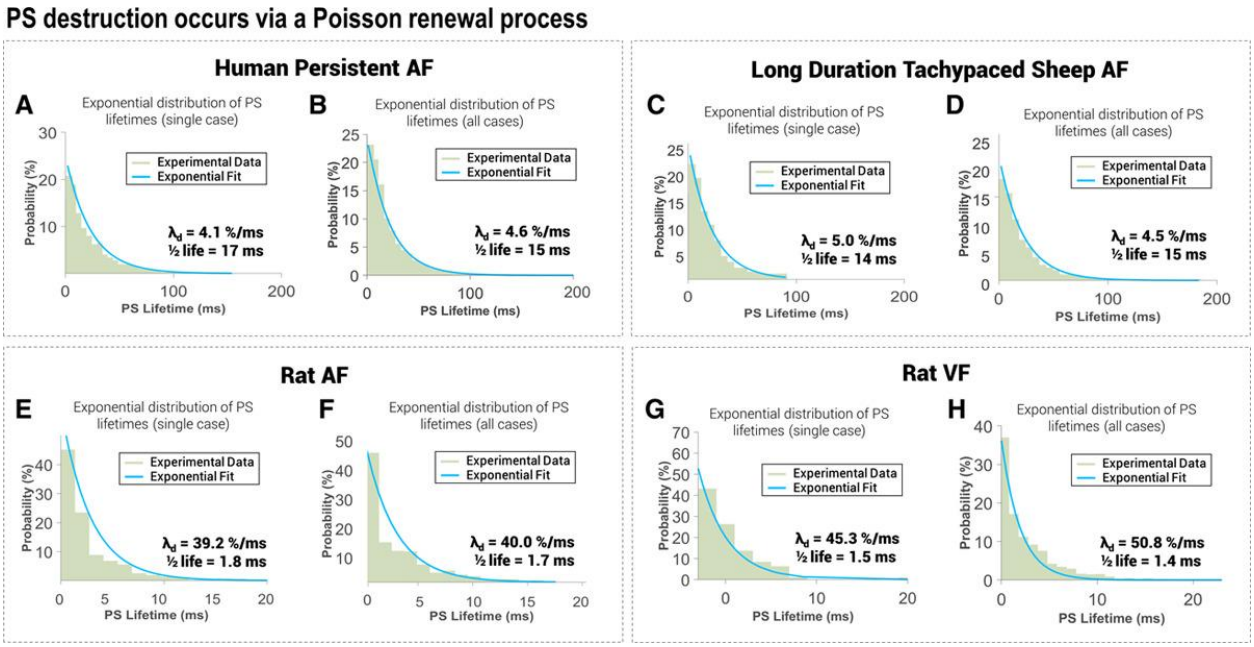
An interesting point to consider is why re-entrant circuits are intrinsically vulnerable to a process of generation and destruction. A clue may be found in the description of a rotor by Winfree. In his seminal monograph on spiral wave dynamics, Winfree provides a critical explanation as to why the generation of new PS occurs: “[Because] every phase of the cycle [is] simultaneously always present… [the] timing of a stimulus is then no longer critical, whenever it will find somewhere a strip of tissue in the critical phase” (458). By the same explanation, because all phases of the cycle are simultaneously always present, any PS is intrinsically vulnerable to annihilation by an incoming wavefront. In an arrhythmia with disaggregated and spatially separated PS-like AF, the annihilation of the PS is thus statistically inevitable and accounts

for the destruction of PS. This explains the exponential-type distribution of PS lifetimes that is universally observed in fibrillation.

1.8.5.5 Evidence for a Renewal Theory Approach in Cardiac Fibrillation

Recently, we studied inter-event times for PS formation events and PS lifetimes in several systems. These included human persistent AF (basket catheter mapping) and rat AF (optical mapping)(16). When a probability distribution function of PS lifetimes and inter-formation times were plotted, an exponential distribution of PS inter-formation and lifetimes, consistent with an underlying renewal process was observed in animal, rat and sheep AF and rat VF, with $R^2 \geq 0.90$ in all systems (16).

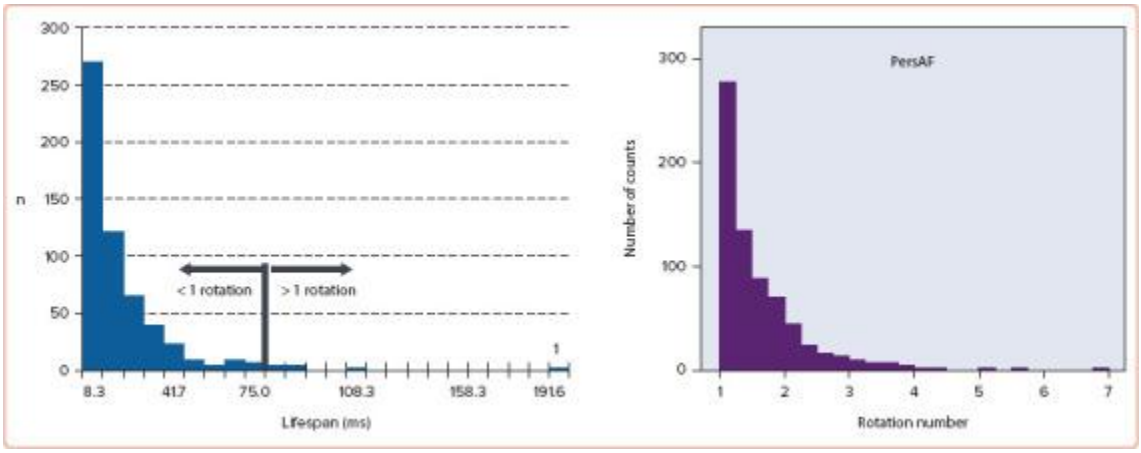
Figure 1.7: Evidence for Renewal Theory in AF



Exponential distribution of phase singularity (PS) inter-formation times and lifetimes in human AF, sheep AF, rat AF and rat VF. Adapted from Dharmaprani et al (16). Used with permission from Wolters Kluwer Health.

Interestingly, when a systematic review was conducted, exponential distribution of PS lifetimes was also observed from six other studies including human AF and VF with PS lifetimes histogram plots, further supporting the notion of cardiac fibrillation as a form of renewal process (82, 459-462) (Figure 3). The first study was from the group of Chen et al., using the classic cholinergic model of AF in the explanted sheep heart, mapped with optical mapping (461). Chen et al. demonstrated that PS in this model had a mean lifespan of 19.5 ± 3.8 ms, and examination of the published histogram of the data from that paper showed the characteristic shape of an exponential distribution (461). Similar findings were observed in another study (82). In that study, rotor lifetimes were examined in epicardial mapped recordings from patients undergoing cardiac surgery, in both persistent and paroxysmal AF (82). Very similar findings have been observed in basket catheter recordings by Child et al (463). We have also identified the same pattern of PS lifetimes in VF from multiple distinguished laboratories (464-466). The convergence of renewal rates of PS formation and destruction conforms with models of spiral wave chaos showing quasi-stationary steady state numbers of PS (467).

Figure 1.8: Evidence of an Exponential Shape of Phase Singularity and Rotor Lifetimes in Two Models of AF



The left panel shows phase singularity (PS) lifetimes from the classical cholinergic model of AF, mapped using optical mapping in the Jalife laboratory (468-471). The right panel shows rotor lifetimes mapped

using epicardial electrogram recordings from human patients at cardiac surgery from the Schötten laboratory (455). In both examples, consistent with our data (Figure 2), an exponential distribution of PS lifetimes and rotors can be seen (16, 457). This is consistent with the notion of quasi-stationary decay dynamics of unstable re-entrant circuits. PersAF = persistent AF.

Mechanistically, this suggests that AF is maintained by continuous formation and destruction of PS. The concept of continuous regeneration of PS is consistent with our current observation on the behaviour of PS in fibrillation. The varying activation times surrounding each PS are susceptible to interaction with incoming waves from other PS, forming wave breaks and new PS, while each PS are also susceptible to destruction through waves from a neighbouring PS (16). Importantly, modelling AF as a renewal process enables the calculation of renewal rate constants, a measurable statistical parameter of the renewal process. We have also shown that these rate constants scale with the area under observation, but that the renewal equations themselves are scale-invariant under scale transformation (457). More recently, Dharmaprani et al demonstrated the utility of renewal theory to analyse and accurately predict PS and wavefront population distribution from human ventricular fibrillation (VF) epicardial sock recordings in human VF (472). The renewal process was used to describe self-terminating episodes of VF which was characterised by slowing of both the rates of formation and destruction of PS (472). Summary of applications of renewal theory in cardiac fibrillation to date as represented in Figure 1.4

1.8.5.6 Applying renewal process to assess phase singularity dynamics

Signal filtering, sinusoidal recomposition and Hilbert transform

Surface ECG, 3D data and unipolar signals were exported and signal processing of intracardiac electrograms was performed as previously described in other studies (463). To allow analysis of only intracardiac atrial electrical signals, QRS subtraction was performed to remove ventricular contamination of intracardiac unipolar signals, using template matching method previously described by Shkurovich

(473) and detection algorithm by Pan and Tomkins (474). QRS subtracted signals were then filtered using fourth order Butterworth at 1 to 30 Hz band pass filter in the forward and reverse mode (459).

To allow phase reconstruction of electrical signals using Hilbert transform (475), sinusoidal recomposition of filtered atrial signals was initially performed. Sinusoidal recomposition of atrial signals transforms these signals into sinusoidal wavelets: -

1) Negative slope of the original unipolar signals corresponding to the amplitude of the signal
2) Time of each sinusoidal signal corresponding to the cycle length of the atrial electrogram, derived from dominant frequency analysis of the respective electrogram

Hilbert transform is then applied to each of the filtered and sinusoidally recomposed signals for phase reconstruction of the collected atrial electrograms. Hilbert transform can be mathematically determined as follows:

$$\phi(t) = arctan\left(\frac{-u(t) - u*}{H(u)(t) - u*}\right)$$

Where u* is the origin of the phase plane with respect to the computed phase

Phase singularity detection method

In RENEWAL-AF, we employed the double ring extended topological charge approach for PS detection. The double ring method consists of an inner 2 x 2 grid, enclosed by an outer 4 by 4 electrode rings. In the smaller 2 by 2 grid, PS is detected if there is presence of a single-phase difference greater than π. PS core is assumed to be the intersection of four pixels in the inner 2 by 2 grid. The presence of PS is confirmed by simultaneous detection of the PS on the inner and outer ring, which results in greater accuracy and noise insensitivity (82).

Figure 1.9: Phase singularity detection on phase map

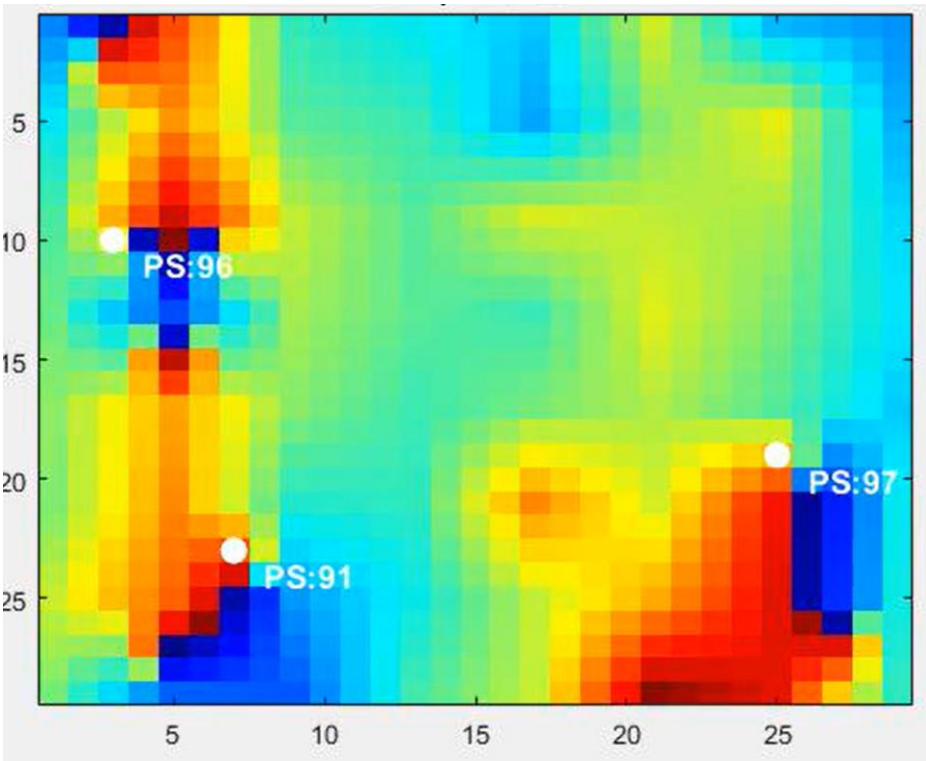


Figure 1.9 showing an example of three phase singularities detected on a phase map obtained from HD grid mapping of the LA posterior wall.

Phase singularity look up table

A look up table indexing onset time, offset time and electrode location were created for each new PS detection to determine PS lifetime and PS inter-formation event times. In RENEWAL-AF, detection of new PS event was defined as detection of a PS at an electrode and its neighbouring one electrode for 20 consecutive frames, corresponding to a duration of 10 ms. Through the look up table, histograms are computed for PS lifetimes and inter-formation times (447).

Renewal process models

In RENEWAL-AF, the dynamics of PS destruction and formation were modelled as renewal processes. In this framework, the waiting time for an existing PS to be destroyed (lifetime) and the waiting time between the creation of new PSs (inter-formation time) are treated as random variables. These times are assumed to follow an exponential distribution, defined by a rate parameter, λ. The probability density function (PDF) for these times is:

$$f(t) = \begin{cases} 0 & t < 0 \\ \lambda e^{-\lambda t} & t \geq 0 \end{cases}$$

where *t* is time. The specific rates for PS destruction and formation are distinguished as λd and λf, respectively.

Parameter Estimation and Model Validation

The rate parameters, λd and λf were estimated using two independent methods to ensure robustness.

1. **Non-linear Least Squares Fitting:** The data were first binned into normalized histograms to represent the empirical PDF. An exponential curve was then fitted to this histogram in Matlab using the Trust-Region algorithm (tolerance: 1E-8, max iterations: 400). The goodness-of-fit for this method was quantified using the R^2 value, Sum of Squares Error (SSE), and Root Mean Square Error (RMSE).

2. **Maximum Likelihood Fitting**: As a comparative method, we employed maximum likelihood estimation. This approach offers a key advantage by fitting the model directly to the raw, unbinned data, thereby avoiding potential biases introduced by histogram binning choices. The fit was performed in Matlab, and its adequacy was assessed with a chi-squared (χ^2) goodness-of-fit test. This test evaluates the null hypothesis that the data originates from an exponential distribution; a p-value ≥ 0.05 fails to reject this hypothesis, indicating a good fit.

1.8.5.7 Potential Applications of the Renewal Paradigm in Mechanistic Studies

The renewal process paradigm could be used in several contexts to quantify the dynamics of fibrillation. From a diagnostic benefit, it allows the reclassification of patients from an outdated, temporally based classification of AF which does not relate to a patient's underlying AF pathobiology, to one that reflects underlying electrical and structural remodelling. This can be achieved by extending the application of renewal process assessment from surface ECG, hence allowing this to be measured in an outpatient (OPD) setting. In addition, it would also allow progression of AF to be monitored in an OPD setting, or to assess if a drug therapy is working for a patient, hence allowing earlier interventions or modifications to therapy by the treating physician. Renewal rate constants obtained could also be used to predict adverse outcomes such as stroke, hospitalisations, and heart failure.

From a therapeutic perspective, intra-operative real-time assessments of rate constants could be beneficial to assist operators to decide what is the best ablation strategy for patients through modulation of the rate constants. In patients undergoing re-do AF ablation procedure, simulation models of their rate constants could be created based on the spatiotemporal distribution of these rate constants, along with the degree of change, which will allow detailed planning regarding the strategy of choice before the re-do ablation procedure. Finally, from a research perspective, it will also allow computer simulations looking at the effect of new therapies and their efficacy on these rate constants, to assess the efficacy of the treatment.

1.8.5.8 Analysis of cardiac fibrillatory signals using other statistical methods.

Besides the renewal approach, the use of other statistical methods to analyse cardiac fibrillatory signals have been previously described.

Stochastic trajectory analysis of ranked signals mapping method uses data obtained from multiple individual wavefront trajectories and creates a statistical picture from which it determines the

predominant direction of wavefront propagation which allows it to identify atrial regions that most often precede activation of neighbouring sites. For an atrial region to be classified as the earliest atrial site of activation, it was required to lead for ≥75% of wavefronts during a recording period (476).

Some early studies utilising the STAR mapping method have suggested potential clinical efficacy of this method. In 36 patients with persistent AF undergoing AF ablation, the STAR mapping method identified 2.6 ± 0.8 drivers or early sites of activation per patient. Radiofrequency ablation at these locations, in addition to PVI, was associated with an 80% arrhythmia-free survival rate at a mean follow-up of 18.5 ± 3.7 months off anti-arrhythmic drug therapy and without empiric lines (477)

A further prospective study utilising the STAR method in 27 patients with persistent AF, showed up to 83 potential AF drivers, with a mean of 3.1±1.1 drivers per patient, and 70 were targeted for ablation. In 54 patients, a positive ablation response, defined as AF termination in 21 patients or AF cycle length slowing in 33 patients was observed. After a mean of 17 months follow up, 81.5% of patients who underwent STAR guided ablation were free of any atrial tachyarrhythmias and were off antiarrhythmic drugs (478). However, current limitations of using this mapping method to guide ablation strategy include the lack of results from a randomised clinical study.

Another recently proposed statistical method for cardiac fibrillatory analysis includes the use of Granger causality analysis (479). Granger causality uses complex time series analysis derived from electrical signals collected from multielectrode catheters to determine causal relationships between different neighbouring regions to localise areas of high spatiotemporal stability (479). Regions of high spatiotemporal stability are believed to be the drivers for atrial fibrillation. Granger causality was initially used to analyse fibrillatory signals temporal dependence in rat VF models and was subsequently validated in VF optical mapping recordings in human donor LV wedge preparations and AF signals in a small cohort of patients with persistent AF (479). The benefit of using Granger causality is that it overcomes the

limitations of phase mapping in terms of spatial resolution and atrial coverage. However, the use of Granger causality clinically to guide ablation targets have not been validated in any prospective or randomised clinical studies.

1.9 Interatrial conduction of fibrillation.

Electrical conduction from the sinus node to the atrioventricular node and subsequently to the left atrium occurs via three major interatrial pathways 1) Bachmann's bundle 2) interatrial septum and 3) inferior interatrial routes (480). There are also other interatrial pathways involved in electrical conduction from the right atria to the left atria that are present but less studied, including the septo-pulmonary bundle (connecting the right atrium to the left atrial roof) and the septo-atrial bundle (connecting the interatrial septum to the left atrial appendage) (480). Impaired electrical conduction or conduction block through these interatrial pathways, which occurs because of atrial structural remodelling has previously been associated with both AF and supraventricular tachycardias (481-483). Importantly, the potential therapeutic implications of modulating these interatrial pathways have recently been demonstrated by Lim et al. Using 3D computational modelling of AF, complete disconnection of all three major interatrial pathways resulted in changes in the dominant frequency in the left atrium and an increased chance of AF termination by up to 80% (484).

1.9.1 Bachmann's bundle

Bachmann's bundle is an interatrial muscular bundle that connects the left and right atrium and has been thought to play a major role in interatrial conduction. Anatomically, it connects the right atrial appendage, transverses the interatrial groove to the left atrium, superiorly, to the neck of the left atrial appendage and inferiorly to the left lateral ridge, just anterior to the left-sided pulmonary veins (485). Bachmann's bundle receives its vascular supply from the right sinoatrial node, a branch of the right coronary artery in 55% of patients and from the left sinoatrial node, a branch of the ramus circumflex in 45% of patients

(150). Embryologically, it has been shown that Bachmann's bundle arises from similar origins to the normal atrioventricular conduction system, further supporting its potential role in the initiation of atrial tachyarrhythmias (150).

Electrical conduction through the Bachmann's bundle during sinus rhythm is predominantly right to left but variability in electrical conduction has been observed (486). In a study by Teuwen et al using high-resolution epicardial mapping in patients undergoing coronary artery bypass grafting, 67% of patients demonstrated a right to left conduction, while in the remaining patients, electrical activation was from the middle or left side of the Bachmann's bundle (486). Interestingly, it was also noted that conduction block in the Bachmann's bundle was as high as 75%, more common in patients with a history of AF than patients without (3.2% versus 0.9%, P=0.03) (486). In addition, higher degrees of conduction block of above 4% were also associated with a higher incidence of postoperative atrial fibrillation (486).

When considering all the available interatrial routes for electrical conduction, some studies have suggested that preferential conduction over Bachmann's bundle (487, 488) while other studies suggest that other interatrial routes, such as the inferior interatrial route plays a dominant role (141, 489). However, studies looking at left-to-right electrical conduction during fibrillation remain limited. The only study looking at this was performed by Kumagai et al which showed preferential fibrillatory conduction via Bachmann's bundle (481). Changes in the electrophysiological properties of Bachmann's bundle have been thought to play a role in the initiation of atrial tachyarrhythmias. In animal models, Waldo et al showed changes in the P wave morphology and duration in canine models with surgical lesions on the right and left portion of the Bachmann's bundle. Prolongation of the P wave duration in this setting was thought to be secondary to the presence of interatrial block, defined as a P wave duration of > 110 ms. Additionally, a biphasic P wave morphology in a partial interatrial block is thought to be secondary to unequal activation of both the left and right atria, while positive and negative deflection in the P wave morphology in advanced interatrial block is secondary to the preferential conduction from the RA to the

LA via the AV node. In patients with interatrial conduction block, histological studies have shown the presence of fibrosis in Bachmann's bundle.

Earlier animal model studies have provided crucial insight into the role of Bachmann's bundle in the initiation and maintenance of AF. In n=6 canine models with sterile pericarditis, preferential fibrillatory conduction was observed during episodes of induced AF through the interatrial septum, particularly through the Bachmann's bundle (481). In another study by Ogawa et al, in n=17 canine models with induced AF, premature left atrial beats generated in the high left atrium was conducted slowly to the right atrium and subsequently, resulted in echo beats in the left atrium. Combined with the observation of fragmented electrograms in Bachmann's bundle, Ogawa et al suggested the presence of functional electrical dissociation resulted in the formation of Bachmann's bundle re-entry, which is a known precursor for AF (149). A recent observation from a retrospective study has further reinforced the electrical associations between atrial regions connected by Bachmann's bundle. In this study involving n=20 AF patients who were thought to have AF originating from the RAA (defined as patients with AF termination through ablation around the RAA), AF cycle length was the shortest in the RAA, followed by LA roof region and LAA, even when compared to other sampled RA locations (490). Structurally, thick sagittal bundles were observed within the RAA using intracardiac echocardiography and pacing of these bundles resulted in leftward electrical conduction from the RAA to crista terminalis followed by the left atrial roof and LAA region. The authors argued that collectively, these findings can be explained by the dominant role of the RAA, crista terminalis and Bachmann's bundle in interatrial conduction (490).

Studies looking at active intervention to Bachmann's bundle in the form of pacing or ablation have so far shown mixed results. An earlier study involving n=120 patients receiving pacemaker for standard pacing indications were randomised to either right atrial appendage or Bachmann's bundle region pacing. After followed up of 12.6 ± 7.4 months, patients randomised to Bachmann's bundle region pacing had a higher freedom from AF compared to patients with right atrial appendage pacing (75% vs 47%, $P<0.005$) (491).

However, another study involving n=30 patients with myotonic dystrophy receiving pacemaker randomised to Bachmann's bundle pacing versus right atrial appendage pacing failed to show any significant differences in the number and duration of AF episodes (492). A more recent meta-analysis involving twelve randomised controlled studies involving n=1146 patients randomised to either interatrial septum pacing or right atrial appendage pacing showed lower AF burden (P=0.008) and lower number of AF episodes (P=0.05) in patients randomised to interatrial septum pacing but no difference in the occurrence of AF (P=0.58) (493). Although catheter ablation in left atrial regions of Bachmann's bundle has been described, no significant differences in freedom from AF (P=0.2) were observed in a small prospective study involving n=68 patients undergoing AF ablation after 12 months follow up (494). Similarly, while limited evidence exists in the realm of surgical isolation of Bachmann's bundle in AF patients, a small observational study involving n=30 AF patients who underwent Bachmann's bundle surgical isolation showed freedom from AF in 87% of patients after one year follow up (495).

1.9.2 Interatrial septum

Anatomically, the left atrium is separated from the right atrium by a fibromuscular structure, known as the interatrial septum. The true interatrial septum comprises of the fossa ovalis and a surrounding muscular rim, also known as the limbus (496). It is bounded superiorly between the superior vena cava and the right sided pulmonary veins and posteriorly, by the coronary sinus (480). It is innervated by sympathetic fibres, originating from the external stellate ganglion, which could be of relevance to the pathogenesis of AF (497). Electrically, the anterior and middle internodal tracts which connects the sinoatrial node and the atrioventricular node courses through the anterior and posterior aspect of the interatrial septum, respectively (498). In canine models, the presence of specialised excitable atrial muscular fibres in the interatrial septum have been demonstrated during pharmacologically-induced atrial arrest (499).

In sinus rhythm, simultaneous biatrial basket catheter mapping in canine models have revealed discordant activation of the atrium, with the left atrium activation approximately 17 ± 7 ms later than the right atrium (500). In human models, similar observations have been made by Lemery et al who showed 1) left septal activation occurred significantly later than right septal activation (22 ms, $P<0.0001$) and 2) mean right septal activation occurred significantly longer than the left atrium (48 ± 14 ms versus 33 ± 9 ms, $P<0.001$) (487).

In AF, using 372 unipolar electrodes recorded simultaneously from both atrial free walls, Kumagai et al showed the presence of unstable re-entrant circuits clustered predominantly around the interatrial septum during AF, with the propagation of wavefronts from the interatrial septum to the Bachmann's bundle in n=6 canine models with sterile pericarditis (481). From this study, Kumagai et al concluded that the interatrial septum played an important role in the maintenance of AF (481). Mechanistically, this is thought to be secondary to the formation of fibrosis and subsequently, re-entrant circuits around the interatrial septum region. For instance, Candales et al observed in n=105 patients who were referred for a transesophageal echocardiogram for multiple medical reasons, increased interseptal thickness was an independent predictor with the presence of AF (501). This suggests underlying structural changes in the interatrial septum may play an important role in the initiation of AF. Similar findings were made by Park et al, who observed an increased extent of complex fractionated electrograms in the left atrium in n=71 AF patients with higher degrees of interatrial septal thickness, measured on cardiac computed tomography scan (502). Importantly, an increased interatrial septal thickness was associated with lower acute procedural success in AF patients undergoing catheter ablation (502).

From a therapeutic perspective, Tondo et al showed that linear radiofrequency ablation transversing the mid-interatrial septum between the fossa ovalis and the inferior vena cava could render AF non-inducible in n=11 canine models (503). In human AF, a prospective randomised study involving n=200 patients with paroxysmal AF randomised to pulmonary vein isolation versus pulmonary vein isolation plus additional

linear ablations from the superior vena cava to the right atrial septum, patients who received additional linear ablation to the septal region had a significantly lower rate of AF recurrence compared to control (6% versus 27%, P<0.001, respectively), after a mean of 12 months follow up (504). In another observational study involving n=2140 AF patients who underwent AF ablation, after a mean of 40 months follow-up, patients who received additional ablation to the right atrial septum had improved freedom from atrial tachyarrhythmias when compared to patients without additional ablation in a propensity-matched score(P<0.001) (505). Interatrial septal pacing, in addition, has been shown to significantly reduce symptomatic occurrences of AF and shorten the mean P wave duration in an observational study involving n=25 patients with sinus bradycardia and paroxysmal AF (82 ± 15 ms versus 118 ± 17 ms, P<0.001) (506). However, results from this study have not been demonstrated in other studies, which found equivocal clinical benefits of interatrial septal pacing (507, 508).

1.9.3 Inferior interatrial routes

Some studies have suggested the predominant role of inferior interatrial routes in interatrial conduction. A comprehensive histological study involving n=21 sliced necropsied human hearts investigating anatomical relationships between the right atrium and the left atrium has previously been performed by Mitrofanova et al (509). Anatomically, muscular sleeves were found extending from the right atrium and wrapping around the proximal coronary sinus in a majority of patients (509). Lack of continuous layers of smooth muscle cells in the media of the coronary sinus wall goes against potential electrical conduction via coronary sinus wall, as a possible route for interatrial electrical conduction (509). However, only in half of these patients, a potential right to left electrical conduction is possible through extension of the muscular sleeves into the inferior wall of the coronary sinus, which allows a connection with the inferior septal region of the left atrium (509). Interestingly, the presence of neural ganglia in the epicardial fat pad in the inferior interatrial groove has also been demonstrated, with proximity to these muscular bundles, which could indirectly influence electrical propagation through these muscular bundles (509). Another

study has also observe the presence of rapid bursts of electrical activities arising from the coronary sinus, faster than that in the atria that initiated episodes of AF, suggesting the coronary sinus may have similar electrophysiological properties to that of the pulmonary veins (510).

Electrically, it has been demonstrated in a small study of n=17 patients without a history of AF, electrical conduction delay was present around the inferior right atrium, around the posterior region of the triangle of Koch in patients whom AF was inducible (511). Similar observations were made in another study by Platonov et al in 2001 (512). In this study, endocardial recordings were collected from n=21 patients with lone AF and n=23 control patients (patients with history of AV nodal re-entrant tachycardia but no history of AF) during sinus rhythm and during programmed atrial stimulation. It was observed that the interatrial conduction time was significantly longer in patients with AF due to longer conduction time between the high lateral right atrium and the proximal coronary sinus, in both sinus rhythm and during programmed atrial stimulation (512). In sinus rhythm, limited evidence has suggested the potential superior role of the inferior interatrial route over the Bachmann's bundle, as the preferred route for interatrial conduction. A study by Markides et al involving n=21 paroxysmal AF patients who underwent non-contact endocardial mapping during sinus rhythm showed earliest endocardial LA breakthrough occurring around the posteroseptal region (around the region of coronary sinus) in 53% of patients compared to 37% of patients, where earliest endocardial breakthrough was seen around the anterosuperior LA wall (around the region of Bachmann's bundle) (141). In another study, high density endocardial mapping was performed in n=9 AF patients prior to ablation, showed the earliest site of activation were in the left posteroseptal wall, just adjacent to the right pulmonary veins, consistent with a predominant role of inferior interatrial routes in interatrial electrical conduction and to a lesser extent, the anterosuperior region of the LA, which corresponds to the region of insertion of the Bachmann's bundle (489). However, another study utilising electroanatomic mapping during left atrial distal coronary sinus pacing (left to right electrical activation) in =18 patients who underwent electrophysiological studies revealed the earliest site

of activation being the coronary sinus os, followed by the fossa ovalis and the high right atrium, presumed to be the site of insertion of the Bachmann's bundle (513).

Given the plausible role of the coronary sinus, via the inferior interatrial route in AF maintenance, a few studies investigating clinical outcomes of coronary sinus ablation have been performed. In canine models of AF, using an optical mapping system, Morita et al demonstrated that coronary sleeve musculature could contribute to unstable re-entry and subsequently, AF and coronary sinus isolation in canine models resulted in termination and non-inducibility of AF (514). In n=45 AF patients undergoing the PVI procedure, endocardial and epicardial ablation of the coronary sinus were performed if AF persisted after the PVI procedure. The endpoint of coronary sinus ablation was CS electrograms with shorter cycle lengths than that of the left atrial appendage (515). This study showed that in n=16 or 35% of patients, coronary sinus ablation was associated with a significant prolongation of fibrillatory cycle lengths and subsequent termination of AF in these patients (516). Similarly, in an earlier study by Oral et al involving n=22 paroxysmal AF patients who underwent PVI-only procedure, coronary sinus isolation reduced AF inducibility post-procedure by up to 67%, suggesting a potential clinical benefit from coronary sinus isolation (510). No randomised control studies have been carried out to date looking at the incremental benefit of coronary sinus isolation, in addition to PVI in AF patients.

Chapter 2

Role of interatrial conduction in atrial fibrillation. Mechanistic insights from renewal theory-based fibrillatory dynamic analysis.

Peer reviewed publications

Quah JX, Jenkins E, Dharmaprani D, Tiver K, Smith C, Hecker T, Joseph MX, Selvanayagam JB, Tung M, Stanton T, Ahmad W, Stoyanov N, Lahiri A, Chahadi F, Singleton C, Ganesan A. Role of interatrial conduction in atrial fibrillation: Mechanistic insights from renewal theory-based fibrillatory dynamic analysis. Heart Rhythm O2. 2022 May 16;3(4):335-343.

Poster presentation HRS 2022: PO-641-06 ROLE OF INTERATRIAL CONDUCTION IN ATRIAL FIBRILLATION. MECHANISTIC INSIGHTS FROM RENEWAL THEORY-BASED FIBRILLATORY DYNAMIC ANALYSIs. Alvin Quah, B Med Sc, MBBS, FRACP. DOI: https://doi.org/10.1016/j.hrthm.2022.03.150

2.1 Abstract

Background: Inter-atrial conduction has been postulated to play an important role in atrial fibrillation (AF). The pathways involved in inter-atrial conduction during AF remain incompletely defined. We recently showed physiological assessment of fibrillatory dynamics could be performed using renewal theory, which determines rates of phase singularity formation (λ_f) and destruction (λ_d). Using the renewal approach, we aimed to understand the role of the inter-atrial septum and other electrically coupled regions during AF.

Methods: RENEWAL-AF is a prospective multicenter observational study recruiting AF ablation patients (ACTRN 12619001172190). We studied unipolar electrograms obtained from sixteen biatrial locations prior to ablation using a 16-electrode Advisor^{TM} HD-Grid catheter. Renewal rate constants λ_f and λ_d were calculated, and the relationships between these rate constants in regions of inter-atrial connectivity were examined.

Results: N=41 AF (28.5% females) patients were recruited. A positive linear correlation was observed between λ_f and λ_d (i) across the inter-atrial septum (λ_f r^2=0.5, P<0.001, λ_d r^2=0.45, P<0.001); (ii) regions connected by Bachmann's bundle (RAA-LAA λ_f r^2=0.29, P=0.001; λ_d r^2=0.2, P=0.008) and (iii) the inferior inter-atrial routes (CTI-LA septum λ_f r^2=0.67, P<0.001; λ_d r^2=0.55, P<0.001). Persistent AF status and LA volume were found to be important effect modifiers of the degree of inter-atrial renewal rate statistical correlation.

Conclusions:

Our findings support the role of interseptal statistically determined electrical disrelation in sustaining AF. Additionally, renewal theory identified preferential conduction through specific inter-atrial pathways during fibrillation. These findings may be of importance in identifying clinically significant targets for ablation in AF patients.

2.2 Figure 2.1: Central illustration

Figure 2.1: Renewal theory concept and its application to fibrillatory dynamic analysis in anatomically and electrically coupled atrial regions.

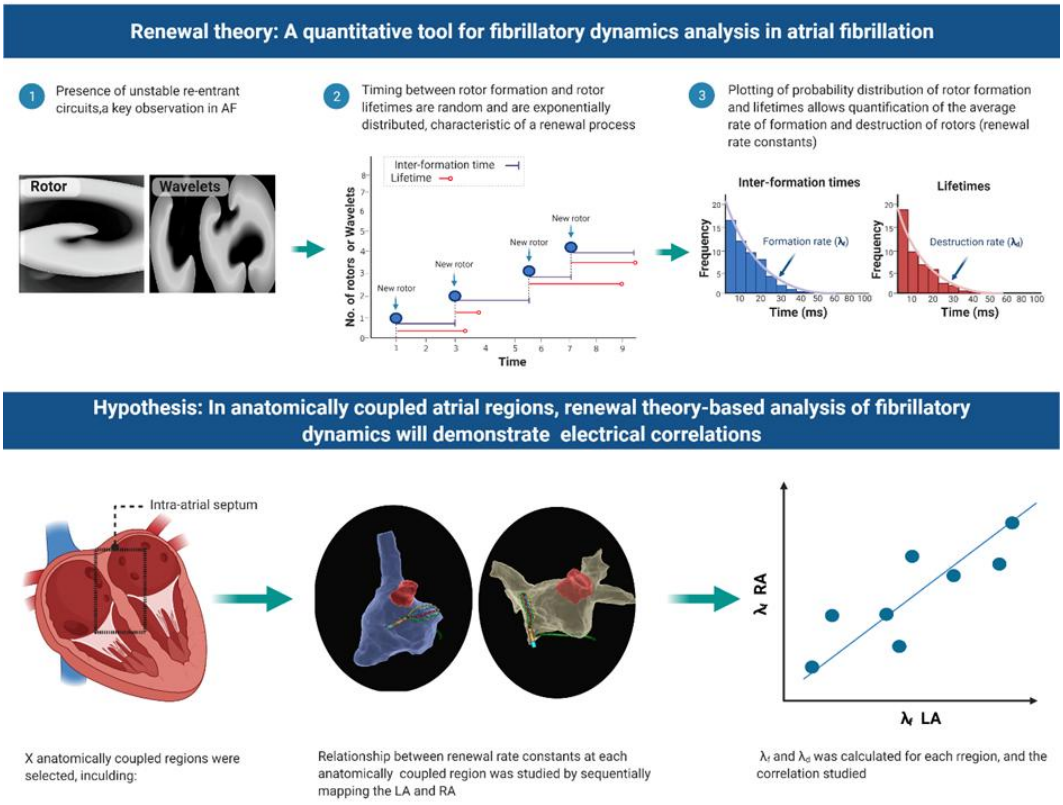


Figure 2.1 – Introduction to renewal theory. (1) Renewal theory is based on the presence of unstable re-entrant circuits, currently believed to be spiral waves in AF. (2) The intervals between phase singularity (PS) formation events and the lifetimes of PS are measured, and distributions for these constructed. (3) These have been shown to be statistically independent, and form exponential distributions, implying a constant rate of PS formation (which we call λ_f and λ_d). The hypothesis evaluated in this study was that anatomically connected bi-atrial regions would show a linear correlation between λ_f and λ_d.

2.3 Introduction

A mechanistic role for inter-atrial connections in atrial fibrillation (AF) maintenance has been postulated (481, 503, 517, 518). However, to date, the precise mechanisms by which inter-atrial

conduction plays a part in sustaining AF have not been fully defined (517, 518). A potential barrier to delineating the role of inter-atrial conduction in AF perpetuation has been that it has been challenging to physiologically probe these connections during sustained AF due to the turbulent nature of the fibrillatory process.

To date, inter-atrial conduction has been proposed to contribute to several divergent but important roles in sustaining AF. Mechanistically, inter-atrial connections have been suggested to be: (i) potential sources of re-entrant circuits;(481, 519) (ii) potential sites of conduction block that could assist in sustaining AF (150, 486). There has also been interest in a potential therapeutic effect of modifying inter-atrial conduction via catheter ablation, in both experimental(481, 503) and computational models.(484)

In this study, we sought to extend previous research by systematic evaluation of inter-atrial conduction during AF in humans using a renewal theory approach. Renewal theory provides a way to measure the continuous formation and destruction of unstable re-entrant circuits in AF(16, 457, 520) and VF(457). Unstable re-entrant circuits, at present believed to be spiral vortices,(521, 522) have been consistently observed in AF research (75, 461, 463, 481, 523, 524) .

The repetitive creation and annihilation of spiral waves observed in AF is parallel to other turbulent systems in nature.(525-528) Theoretically, it has been proposed that in systems characterised spatiotemporal turbulence, spiral dynamics will follow a common set of statistical laws (528), namely that: (i) spiral lifetimes will follow exponential distributions (467, 528, 529) and (ii) spiral populations will follow a Poisson distribution (467, 530). These predictions have been independently validated in diverse physical (526), chemical (527) and biological systems (525, 528). In the context of fibrillation, exponential-type distributions have consistently been observed for phase singularities (PS) formation, as well as PS lifetimes in multiple laboratories (82, 460, 461, 463, 531). In computational, animal and human models of cardiac

fibrillation, using the renewal theory approach,(16, 457, 472, 520) we confirmed these observations and demonstrated it could allow for accurate quantification of rates of PS formation (λ_f, pronounced as lambda 'f') and destruction of PS (λ_d, pronounced as lambda 'd') (16, 457, 472) (Figure 1). We found that although the renewal rate constants scaled with catheter size (472), the renewal equations for population distribution remained internally consistent (472), in line with theoretical predictions about the effect of noise (532), and 3-dimensional character of cardiac turbulence (533). A summary figure explaining renewal theory is provided in Figure 1.

In the current study, we build on this earlier work by aiming to determine whether renewal theory could be applied to further understand the electrophysiological relationships between the left and right atria. We hypothesised that: (i) atrial regions with anatomical contiguity across the inter-atrial septum should have a positive correlation between respective renewal rate constants; (ii) different patterns of AF could potentially have variable renewal rate constants. We further applied renewal theory to analyse fibrillatory dynamics in other locations involved in inter-atrial conduction, such as the Bachmann's bundle (BB) and the inferior inter-atrial route.

2.4 Methods

Study population

RENEWAL-AF was a multicenter prospective observational study involving four Australian hospitals (ACTRN 12619001172190p). Paroxysmal or persistent AF patients clinically indicated for AF ablation were enrolled. Ethics approval was by the Southern Adelaide Local Health Network Ethics Committee (HREC/19/SAC/292). All patients provided informed consent.

Electrophysiology study

Baseline demographics were obtained pre-procedurally and documented in an electronic clinical record form (Redcap, Vanderbilt University, VA). Electrophysiologic studies were performed five half-lives free of antiarrhythmic drug therapy, except for patients taking amiodarone. Patients were mapped under spontaneous or induced AF using the Ensite Precision electroanatomic mapping system (Abbott Cardiovascular, Plymouth MN). Advisor^{TM} HD-grid mapping catheter was used (Abbott Cardiovascular, Plymouth MN). This catheter has 16 electrodes in a square grid (13x13mm^2 grid, 3mm inter-spacing). Unipolar electrograms were recorded at 1000 Hz (band-pass filter 0.5-500Hz). Electrograms and ECG tracings were recorded for one minute prior to ablation in six different RA intracardiac locations, sequentially; 1) Superior vena cava (SVC)-Right Atrial (RA) junction, cavo-tricuspid isthmus (CTI) , RA septum, RA lateral wall, RA appendage (RAA) and RA posterior; and ten left atrial (LA) locations: 1) Left superior pulmonary vein (LSPV) 2) Left inferior pulmonary vein (LIPV) 3) Right superior pulmonary vein (RSPV) 4) Right inferior pulmonary vein (RIPV) 5) Left high posterior wall 6) Left low posterior wall 7) Left lateral region 8) LA appendage 9) LA anterior region and 10) LA septum (Figure 2.2).

Signal processing

Unipolar electrogram signals were processed as described (16, 457, 472). QRS subtraction was performed, and Butterworth filters applied (16, 457, 472). Sinusoidal recomposition was applied with the dominant frequency set as wavelet period and phase computed using the Hilbert transform to construct phase maps (16, 82, 457, 472). In each phase map, PS were detected and tracked as previously described using a convolution kernel method based on topological charge (16, 457, 472). PS tracking enabled calculation of PS lifetimes and inter-formation times (times between consecutive PS formations), which also enabled construction of PS lifetime and inter-formation time distributions (16, 457, 472). PS distributions were fitted using maximum likelihood fitting to estimate the rate of PS formation (denoted as λ_f) and PS destruction (λ_d) (Figure 2) (16, 457, 472). A description of the processing steps is provided in Figure 2.2.

Statistical analysis

Data was reported as the mean (standard deviation, SD) or the median [interquartile range, IQR] for parametric and non-parametric data. Categorical variables were presented as n (%) and differences between group were examined using the χ^2 test. Two group comparisons were analysed using student t-test. Associations between different anatomical regions were evaluated using Pearson's correlation coefficient. Statistical analysis was performed using STATA 15.1 with α at $P < .05$.

2.5 Results

Patient characteristics

Patient characteristics are described in Table 1. Data from n=41 AF patients who underwent AF ablation were available for analysis. Mean age (years) of patients recruited were 59.1 ± 9.4, 28.5% were females. Mean BMI (kg/m^2) was 31.2 ± 4.4. 41% of patients had paroxysmal AF. Mean CHA_2DS_2-VASc score was 1.9 ± 1.5. Mean left atrial volume index (LAVi) was 42.9 ± 8.5 ml/m^2 (Table 2.1).

Inter-atrial electrical relationships

1. Inter-atrial septum

For this purpose, we compared λ_f and λ_d between RA and LA septal regions (Figure 2.3). Overall, a positive correlation was observed between the λ_f (r^2=0.5, P<0.001) and λ_d (r^2=0.45, P<0.001) between both regions.

Persistent AF status and LA volume were important effect modifiers. Paroxysmal AF showed stronger correlations across the LA and RA septal region (λ_f r^2 =0.72, P<0.001; λ_d r^2=0.79, P<0.001), than persistent AF (λ_f r^2 =0.17, P=0.08; λ_d r^2=0.07, P=0.28). LA volume index had a comparable effect. For patients with LA volume index < 40 ml/m^2, there was a stronger correlation than in patients with LA volume index ≥ 40 ml/m^2. (LAVi < 40 ml/m^2- λ_f r^2=0.68, P<0.001, λ_d r^2=0.68, P<0.001, LAVi ≥ 40 ml/m^2 λ_f r^2=0.27, P=0.03 and r^2=0.14, P=0.14).

2. Bachmann's bundle

Bachmann's bundle is an epicardial muscular bundle that connects the left (LA) and right atrium (RA), and the presence and the extent of conduction block in this structure has been associated with AF incidence and persistence (11, 12). Bachmann's bundle rightward arm crosses the region of cavoatrial junction superiorly around the region of the sagittal bundle, and inferiorly around the subepicardium of the RA vestibule (area between the RA appendage orifice and the RA atrioventricular valve annulus) (11, 13). Bachmann's bundle then courses across the anterior interatrial groove and leftward to the LA appendage,

with muscular fiber projections around the left lateral wall (14, 15). Other studies have suggested the role of high upper septum, which has been shown to form both structural and electrical connection to the mid-portion of the Bachmann's bundle (16). For this study, only endocardial mapping was performed in these patients. Hence, RAA, RA septum and SVC-RA junction were used as surrogates for RA site attachments and LAA and LA lateral wall were used as surrogates for LA site attachments for the Bachmann's bundle.

RAA to LAA and LA lateral wall: A modest linear correlation between LA appendage (LAA) and RA appendages (RAA) (λ_f r^2=0.29, p=0.001) and λ_d of LAA versus λ_d of RAA (r^2=0.2, p=0.008) (Figure 2.4). A modest linear correlation was also observed between λ_f of LA lateral wall and λ_f of RAA (r^2=0.13, p=0.05) and λ_d of LA lateral wall and λ_d of RAA (r^2=0.21, p=0.009) (Figure 2.4).

SVC-RA junction to LAA and LA lateral wall: A modest linear correlation between λ_f of the SVC-RA junction and LAA (λ_f r^2=0.22, p=0.003) and λ_d of LAA versus λ_d of SVC-RA junction (r^2=0.23, p=0.002). A modest linear correlation was also observed between λ_f of LA lateral wall and λ_f of SVC-RA junction (r^2=0.13, p=0.05) and λ_d of LA lateral wall and λ_d of SVC-RA junction (r^2=0.29, p=0.001).

RA septal to LAA and LA lateral wall: A modest linear correlation between RA septal and LAA (λ_f r^2=0.16, p=0.011) and λ_d of LAA versus λ_d of RA septal (r^2=0.11, p=0.04). No significant relationship was observed between λ_f of LA lateral wall and λ_f of RA septal (r^2=0.02, p=0.35) in contrast with a stronger linear correlation observed between λ_d of LA lateral wall and λ_d of RAA (r^2=0.51, p<0.0001).

3. Inferior inter-atrial connections

In this study, the cavo-tricuspid isthmus region was used as indicator of potential inter-atrial conduction in the inferior region of the RA with all six LA atrial regions within the LA atrial body. Positive correlations between RA CTI and a variety of LA regions (λ_f CTI-LA septum r^2=0.67, P<0.001, CTI-LA-lateral wall r^2=0.53,

P<0.001, CTI-LA anterior wall r^2=0.5, P=0.001, CTI-LA low posterior wall r^2=0.42, P=0.001, CTI- LA high posterior wall r^2=0.28, P<0.001. For λ_d, positive correlations were observed between CTI and LA-anterior wall (r^2=0.6, P<0.001), CTI-LA septum (r^2=0.55, P<0.001), CTI-LA-lateral wall (r^2=0.53, P=0.001), CTI-LA low posterior wall (r^2=0.36, P<0.001), CTI- high posterior LA wall (r^2=0.28, P=0.001) (Figure 2.5).

4. **Relationship between spatial variation of global fibrillatory process in the left atrium with the right atrium**

We then analysed the relationship of all RA atrial locations with the mean LA λ_f. Mean LA λ_f was obtained by averaging λ_f of all ten LA locations. Mean LA λ_f showed the highest relationship with CTI region (r^2=0.75, P<0.001) followed by RA septal wall (r^2=0.6, P<0.001), RA lateral wall (r^2=0.5, P<0.001), RAA (r^2=0.34, P<0.001) and SVC-RA junction (r^2=0.32, P<0.001) and RA posterior wall (r^2=0.11, P=0.038) (Table 2.2). Similar observations were made when the relationships between mean LA λ_d were analysed with all six RA locations. Mean LA λ_d showed the highest relationship with CTI region (r^2=0.76, P<0.001) followed by RA septal wall (r^2=0.58, P<0.001), RAA (r^2=0.52, P<0.001), SVC-RA junction (r^2=0.49, P<0.001), RA lateral wall (r^2=0.45, P<0.001), and RA posterior wall (r^2=0.12, P=0.037) (Table 2.3).

When patients were examined according to their paroxysmal-persistent AF status, significant positive correlations were observed between mean LA λ_f with λ_f at the RA septal wall (r^2=0.78, P<0.001) and the CTI region (r^2=0.8, P<0.001) in patients with paroxysmal AF (Table 2.4). However, in those with persistent AF, only a modest correlation was observed in the CTI region (r^2=0.54, P<0.001) followed by RAA (r^2=0.38, P=0.004), RA posterior wall (r^2=0.37, P=0.003), SVC-RA junction (r^2=0.26, P=0.013) and RA septal wall (r^2=0.22, P=0.02) (Table 2.4). In persistent AF patients, no significant relationships were observed between mean LA λ_f with RA lateral wall (r^2=0.1, P=0.17) (Table 2.4).

2.6 Discussion

Role of inter-atrial conduction in atrial fibrillation

Anatomically, bi-atrial electrical propagation occurs via three main pathways 1) Bachmann's bundle 2) inter-atrial septum and 3) inferior inter-atrial connections via coronary sinus [4]. In sinus rhythm, it has been argued that Bachmann's bundle plays the dominant role in inter-atrial electrical conduction (487, 534). while other studies argue for the dominant role of coronary sinus (141, 489). However, there are limited evidence to date describing the contributions of these inter-atrial pathways to electrical propagation during fibrillation, using high-density mapping. To the best of our knowledge, this was a study performed by Kumagai et al who observed preferential conduction of fibrillation via the Bachmann's bundle using sterile pericarditis canine models of AF using simultaneous electrogram recordings from 372 unipolar electrodes (481).

Inter-atrial conduction has been postulated to play a potentially important contribution in AF pathophysiology (150, 481, 486, 502, 517). Increased thickness of the IAS has been linked to the presence of AF and an increased recurrence of AF post ablation (501, 502). Electrically, a predominance of complex fractionated electrograms has been observed clustered around the IAS, correlated with its thickness (502, 524). A highly significant contributory role for AF is as a site for critical conduction block leading to the development and perpetuation of AF, based on n=185 cases mapped intra-operatively in sinus rhythm. (150, 486, 517).Similarly, the presence of conduction block in the Bachmann's bundle has also previously been linked to the initiation and perpetuation of fibrillation in human AF(150, 486, 535).

Role of interatrial septum conduction in atrial fibrillation

Over the last two decades, there has been an increasing interest in the role of the IAS and its potential contributions to atrial tachyarrhythmias including AF. Anatomically, the true IAS is a region of the cardiac

structure that separates the left and right atria, limited to both the region of the fossa ovalis (FO), which is surrounded by a raised muscular rim and the mid-septal region (480). Autopsy studies of the IAS from human hearts revealed the presence of traversing muscular fibers on light microscopy (536, 537) and the presence of P-, T- and Purkinje-like cardiac cells, similar structural characteristics to cells from the region of sinoatrial atrio-ventricular node and human ventricles using electron microscopy analysis (536).

In recent years, there have been significant expansion of clinical studies and advancement in our understanding in the role of interatrial connections. In sinus rhythm, some studies have argued that BB plays the dominant role in interatrial electrical conduction (487, 488) while other studies argue for the dominant role of coronary sinus with this regard (141, 489). In n=50 paroxysmal AF patients, using 3D electroanatomical contact mapping, BB was identified as the major interatrial route in patients who utilised a single interatrial pathway while both BB and the IAS around the FO were utilised in patients who used a combination of interatrial routes (534). However, there are limited evidence to date describing the contributions of these interatrial pathways to electrical propagation during AF (481). In n=6 canine models of AF, Kumagai et al performed simultaneous multisite mapping using 372 unipolar electrodes in both atria, including the IAS. While their group reported that the IAS played a major role in fibrillation through the significant formation of unstable re-entrant circuits in this region, this conclusion was made based on qualitative observation of reactivation of nonactivation zones from wavefronts originating from the septum (481).

The role of the IAS in the maintenance of AF is increasingly recognised (481, 502, 517). Crucially, it has also been suggested that the IAS could be a potential target for catheter ablation in AF (517). Lim et al observed changes in the LA AF wave dynamics using bi-atrial modelling of AF, when ablation of different interatrial conduction pathways including interatrial septal routes were performed, in addition to PVI (484). This study showed with complete disconnection between the RA and LA, AF was terminated in 80% of the cases (484). In canine models, the creation of a linear radiofrequency lesion at the mid IAS between

the FO and inferior vena cava resulted in non-inducibility of AF, suggesting interrupting of the interseptal conduction may prevent AF initiation (503). In human studies, the potential benefit of septal ablation was further suggested by Jin et al who observed an improvement in clinical outcomes two years post AF catheter ablation in n=2140 AF patients receiving SVC isolation with additional linear ablation to the RA septum plus pulmonary vein isolation (PVI) compared to patients receiving PVI alone (505).

Understanding the mechanisms of fibrillatory propagation across inter-atrial connections is crucial to define clinically significant atrial regions that could be targeted during catheter ablation in AF (517, 518). Inter-atrial conduction has been suggested a potential target for catheter ablation in AF (517). Early experimental studies in animal models suggested that AF dynamics could be modified by ablation in the septum (503, 519). A potential mechanism for this effect was identified physiologically in more contemporary bi-atrial computational models, which demonstrated termination of AF with disconnection of the RA and LA in 80% of cases (484).

Findings from RENEWAL-AF

Our study adds to the literature as the first to apply a statistical-based approach in a clinical setting to explore anatomical and electrical connections during sustained fibrillation. Renewal theory-based analysis of fibrillatory dynamics in the inter-atrial septum and other atrial regions involved with interatrial conductions revealed the following findings:

1. During fibrillation, statistically-determined electrical disrelation between the LA and RA septum is dependent on paroxysmal-persistent status and LA size. Significant statistical electrical disrelation, measured by λ_f and λ_d, was observed in persistent AF patients compared to paroxysmal AF patients and in patients with larger LA size, suggesting interseptal statistical disrelation plays a role in AF persistence.

This observation is in concordance with other studies investigating the associations between structural and electrical changes within the interatrial septum and. Shin et al observed thicker interatrial adipose

tissue in patients with AF, measured using cardiac CT when compared with control (538). In AF patients, degree of thickness of interatrial adipose tissue was closely linked with both AF persistence and LA volume (538). In another prospective study using transesophageal echocardiogram for quantification of interatrial septal thickness, interatrial septum was observed to be significantly thicker, independent of age, weight and height in AF patients, compared with controls (501). Histologically, interatrial septal biopsies obtained from AF patients have shown evidence of lymphomononuclear infiltrates, cardiomyocyte necrosis and patchy fibrosis, when compared with patients without a history of AF (223). When histological analysis of interatrial septal biopsies was compared between paroxysmal and persistent AF patients, a significantly higher burden of atrial tissue C-reactive protein was observed in patients with paroxysmal AF, suggesting local atrial inflammation in the interatrial septal region plays a crucial role in early stages of AF, which may then progress to structural changes suggestive of chronicity as observed by Frustaci et al (223, 539). Electrically, increased interatrial septal thickness has been linked with a significantly higher burden of complex fractionated electrograms (CFAE) and a lower procedural success rate post AF ablation (502). This observation is crucial as CFAEs have previously been associated with atrial regions of conduction slowing or block and sites of wavefront collisions (540, 541).

2. Varying statistical correlations of fibrillatory processes were observed in other anatomically and electrically connected LA and RA regions, likely due to the varying contributions of inter-atrial conduction to RA fibrillatory processes.

3. Highest statistical correlations between rates of PS formation and destruction between the RA and LA during fibrillation were observed in the cavo-tricuspid region, a surrogate for inferior inter-atrial conduction, followed by inter-atrial septum and RAA. Similar observations were made when AF patients were analysed by paroxysmal-persistent status, suggesting the significant role of inferior interatrial conduction in fibrillatory propagation from the LA to the RA.

Insights into the role of Bachmann's bundle in AF

The role of Bachmann's bundle as a route for macro-reentrant atrial flutter has been described (542, 543) and cases of atrial tachycardia arising from the insertion points of Bachmann's bundle has been observed but uncommon (544). It is possible that such atrial arrythmias degenerate into AF in a small proportion of patients. However, a more common scenario is that of the adverse electrical remodelling that predispose to AF occur simultaneously in both the left atrium and Bachmann's bundle, as recently described (545). In addition, histologically, fibrosis and fibrofatty replacement of the Bachmann's bundle have been observed in AF patients compared to control (546). The suggested implications from our study findings would be either 1) electrically correlated regions suggesting preferential conduction of fibrillation through the inferior interatrial routes or 2) significant electrical disrelation, suggesting presence of significant conduction block at the region of the Bachmann's bundle. It remains unclear if targeted ablation to electrically disrelated regions, or even, electrically related regions could be useful, by means of reduction of total surface area available for fibrillatory propagation (547).

Role of interior interatrial routes. Translating mechanistic findings to clinical findings

Extension of myocardial fibers from the coronary sinus (CS), which wraps around the posterior atrio ventricular sulcus, have been shown to be a source of both anatomical and electrical conduction from the LA to the RA (548). Histologically, three different layers were previously observed (endocardium, myocardium and epicardium) in the wall of the CS, differentiating it from other cardiac veins (548). Purkinje like cells have also been observed in the CS myocardium, which may potentially contribute to both AF initiation and maintenance (549). Clinically, an earlier study has shown the potential benefit of ablation around the endocardial and epicardial coronary sinus region, with prolongation of AF cycle length in both paroxysmal and persistent AF patients, resulting in AF termination in 35% of patients who remained in AF post PVI (516). Results from small observational studies performed to date have suggested

the potential clinical importance of CS in AF maintenance, in keeping with the mechanistic findings from our study. In n=22 paroxysmal AF patients (9 of which had inducible AF post PVI procedure), the addition of coronary sinus ablation rendered AF non-inducible in 6 more patients, with 89% of patients remained AF free after a mean of 199 days follow up (510). Similarly, Haissaguire et al showed a high success rates when CS ablation was performed in addition to PVI in n=45 AF patients (n=15 paroxysmal and n=30 persistent), in which 12 out of 15 paroxysmal AF patients and 27 out of 30 persistent AF patients remained AF free after 10 months (516). In a more recent observational study involving n=10 persistent AF patients, CS isolation was associated with 100% freedom from AF recurrence after 6 months follow up (550). However, in addition to PVI and CS isolation, a further mitral, roof and cavo tricuspid isthmus ablation lines were created for all patients (550).

Rationale for using renewal theory approach in assessing interatrial conduction.

The renewal theory approach used in the current study is useful because it provides a conceptual connection between AF and other systems in nature characterised by the repetitive regeneration of PS. The repetitive generation of PS occurs in biological,(525, 528) physical(526, 551) and chemical (527) systems throughout nature. Renewal theory allows the development of a statistical approaches to understand the formation and destruction of PS. Importantly, the distributions identified for PS lifetimes and population distributions have been shown to be equivalent for AF and VF(16, 457, 472) and these other natural systems, suggesting thematic similarities in terms of the underlying processes sustaining spatiotemporal turbulence in these.

Renewal theory: An alternative, statistical based approach to demonstrate electrical dyssynchrony.

The presence of electrical dyssynchrony between the endocardium and epicardium has also been observed and is hypothesised to play a crucial role in AF persistence(552, 553). In animal AF models, endo-epicardial dyssynchrony (EED) has been shown to be present in both acute and persistent forms of AF

(554). In persistent human AF models, the presence of EED has been defined as differences of endo-epicardial activation times of ≥15 ms, differences in wave front directionality or the frequency of epicardial breakthroughs (527, 553, 555, 556). However, a major obstacle remains in determining the optimal cut off difference of endo-epicardial activation times to demonstrate electrical dissociation. While De Groot et al used a cut off of ≥ 15 ms as a marker for dyssynchronous electrical activation (553), Parameswaran and Walters et al more recently used a stringent cut off of ≥ 20 ms in studies involving high density mapping of swine models and human persistent AF (556, 557). The use of renewal theory to demonstrate electrical dyssynchrony provides a robust statistical-based approach which complements currently used quantitative methods by firstly, demonstrating the presence of statistically determined electrical disrelation between two atrial regions and secondly, in those determined to have statistically-determined electrical disrelation, renewal theory further quantifies the degree of electrical dissociation in this cohort. An area currently under active investigation is the application of a renewal-based approach to demonstrate EED, using simultaneous endo-epicardium HD-grid recordings in AF patients undergoing cardiac surgery (ACTRN12621000684820).

Limitations

There were a few limitations to this study. Firstly, this study involves a relatively small number of patients. However, the methodology described based on renewal theory could be applied in larger studies involving more atrial regions to improve atrial surface coverage. Secondly, sampling of the IAS region was limited to the endocardium and performed sequentially. However, sequential mapping is likely to be reasonable with the renewal theory approach as 1) the renewal rate constants are known to be temporally stable for sustained periods of time and 2) this study provides indirect evidence of temporal stability of renewal constants by showing that physiological correlations exist between anatomically connected regions. Finally, we acknowledge that all groups studying AF do not universally accept the notion of phase singularity mapping (558). However, PS dynamics are widely utilised to

understand cardiac fibrillation and comparably spatio-temporally turbulent systems throughout nature (525-528).

2.7 Conclusion

Using a renewal-based approach for fibrillatory dynamic analysis, we observed varying statistically determined electrical relationships between fibrillatory processes in RA regions to electrically and anatomically connected LA regions. Identification of atrial regions which have significant electrical disrelation could be clinically important to select a subset of AF patients who would potentially benefit from targeted ablation to these areas.

2.8 Tables

Table 2.1: Patient baseline demographics

Baseline Demographics	Mean (SD) or n [%]
Age (years)	59.1 (9.4)
BMI (kg/m^2)	31.2 (4.4)
Sex, female [%]	12 [28.5]
Diabetes mellitus [%]	3 [7]
Hypertension [%]	17 [40.5]
Vascular disease [%]	8 [19.5]
Hyperlipidemia [%]	13 [31]
OSA [%]	14 [34]
Heart failure [%]	17 [41.5]
CVA [%]	6 [14]
Smoking history [%]	10 [23.8]
Alcohol intake [%]	27 [64.3]
Alcohol standard drinks/week	5.7 (11.7)
CHA2DS2-VASc score	1.9 (1.5)
Paroxysmal AF [%]	17 [41]
LVEF [%]	57.5 (10.0)
LAVi [ml/m^2]	42.9 (8.5)

Data presented as mean (standard deviation) or n [%]

Table 2.2: Degree and significance, in a descending order, of correlations between λ_f of measured RA locations with mean LA λ_f.

λ_f values of measured RA locations	**Correlation with mean LA λ_f**
CTI	r^2=0.75, P<0.001
Septal RA	r^2=0.6, P<0.001
Lateral RA	r^2=0.5, P<0.001
RAA	r^2=0.34, P<0.001
SVC-RA junction	r^2=0.32, P<0.001
Posterior RA	r^2=0.11 P=0.038

RA, right atrial; LA, left atrial; CTI, cavo-tricuspid isthmus; RAA, right atrial appendage; SVC, superior vena cava.

Table 2.3: Degree and significance, in a descending order, of correlations between λ_d of measured RA locations with mean LA λ_d.

λ_d values of measured RA locations	**Correlation with mean LA λ_d**
CTI	r^2=0.76, P<0.001
Septal RA	r^2=0.58, P<0.001
RAA	r^2=0.52, P<0.001
SVC-RA junction	r^2=0.49, P<0.001
Lateral RA	r^2=0.45, P<0.001
Posterior RA	r^2=0.12, P=0.037

RA, right atrial; LA, left atrial; CTI, cavo-tricuspid isthmus; RAA, right atrial appendage; SVC, superior vena cava.

Table 2.4: Degree and significance of correlations between λ_f of measured RA locations with mean LA λ_f, according to the paroxysmal-persistent AF classification.

λ_f values of measured RA locations	**Correlation with mean LA λ_f Paroxysmal AF (n=18)**	**Correlation with mean LA λ_f Persistent AF (n=23)**
CTI	r^2=0.8, P<0.001	r^2=0.54, P<0.001
Septal RA	r^2=0.78, P<0.001	r^2=0.22, P=0.02
Lateral RA	r^2=0.5, P<0.001	r^2=0.1, P=0.17
RAA	r^2=0.3, P=0.035	r^2=0.38, P=0.004
SVC-RA junction	r^2=0.4, P=0.007	r^2=0.26, P=0.013
Posterior RA	r^2=0.04 P=0.44	r^2=0.37, P=0.003

RA, right atrial; LA, left atrial; CTI, cavo-tricuspid isthmus; RAA, right atrial appendage; SVC, superior vena cava.

2.9 Figures

Figure 2.2: Determination of λ_f and λ_d from phase singularity inter-formation and lifetimes plots

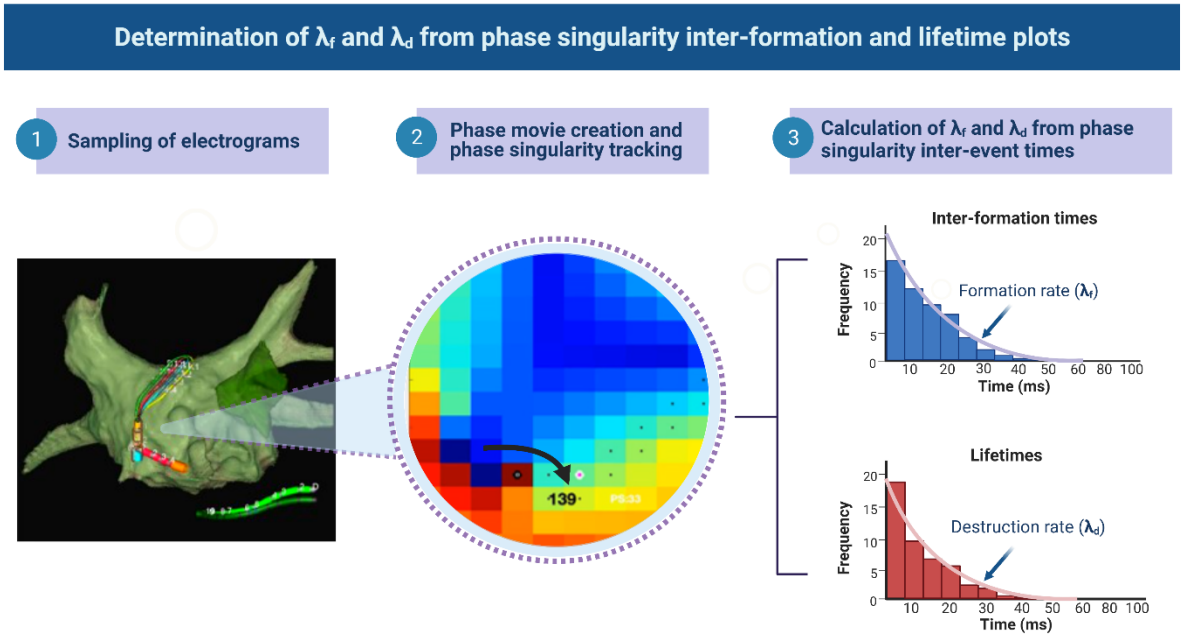


Figure 2.2 - λ_f and λ_d was determined as follows: (1) Unipolar electrograms in AF were sampled pre-ablation in 16 pre-defined biatrial segments (one-minute recordings) with an Advisor™ HD-Grid catheter. Phase movies were created (2), and renewal rate constants calculated for formation and destruction (3).

Figure 2.3: Correlations between λ_f and λ_d on the LA and RA septum

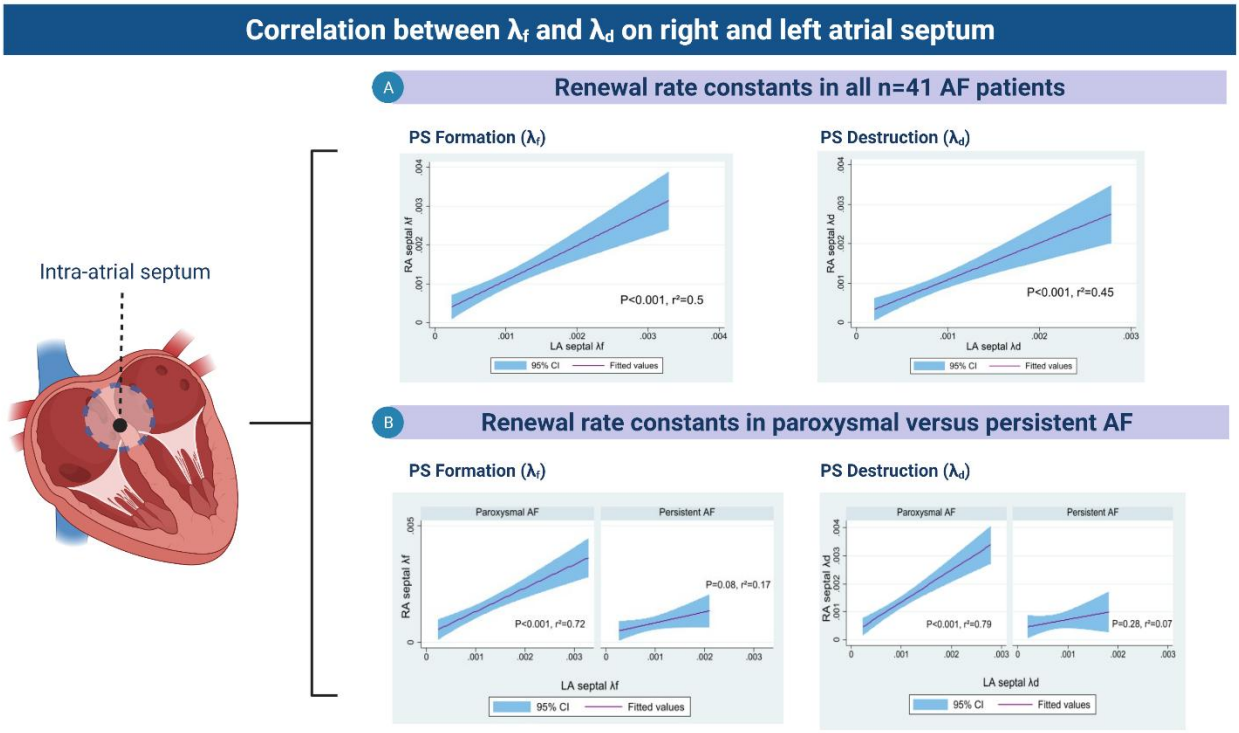


Figure 2.3 – Interseptal conduction showed a positive linear correlation between the right and left side of the inter-atrial septum, an effect that was diminished in patients with persistent AF.

Figure 2.4: Correlations between λ_f and λ_d in the atrial regions connected by Bachmann's bundle.

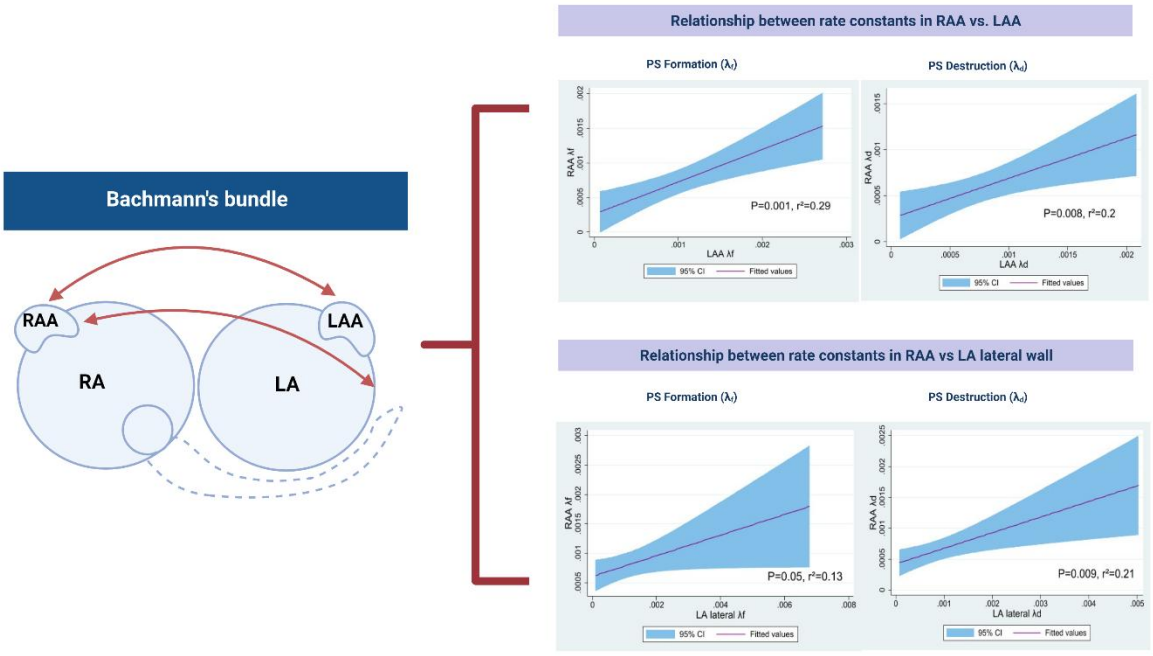


Figure 2.4 – The correlations between left and right atrial appendages and between left atrial lateral wall and right atrial appendages λ_f and λ_d was used as an index for inter-atrial conduction via Bachmann's bundle. This showed a positive linear correlation.

Figure 2.5: Correlations between λ_f and λ_d in the LA atrial regions connected by inferior inter-atrial routes.

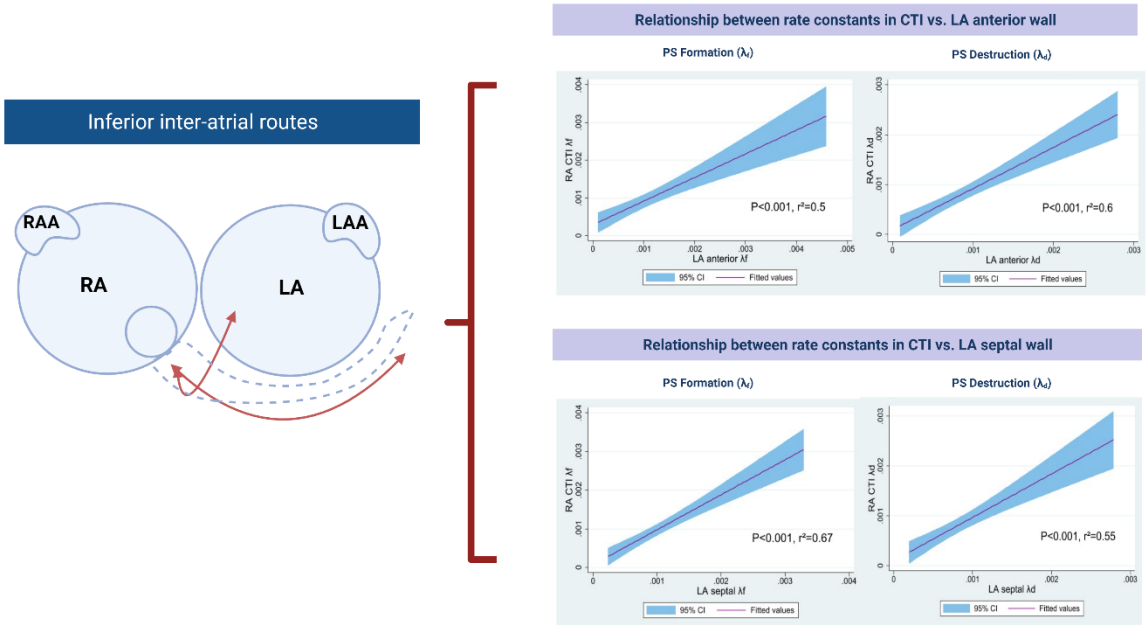


Figure 2.5 – The correlations between the cavotricuspid isthmus and the LA septum/anterior regions λ_f and λ_d were used as an index for inter-atrial conduction via inferior inter-atrial routes. This showed a positive linear correlation.

Chapter 3

Spatial gradient of renewal rate constants at the pulmonary vein-left atrial junction: associations with the clinical outcomes of atrial fibrillation ablation

Peer review publication

Oral presentation Heart Rhythm Society May 2022: CA-529-01 RENEWAL THEORY: A STATISTICAL APPROACH TO IMPROVE PATIENT SELECTION FOR PULMONARY VEIN ISOLATION-ONLY STRATEGY IN ATRIAL FIBRILLATION ABLATION. DOI: https://doi.org/10.1016/j.hrthm.2022.03.120

3.1 Abstract

Aims: Outcomes from pulmonary vein isolation (PVI) in atrial fibrillation (AF) remain suboptimal, especially in persistent AF, suggesting the need for new electrophysiological characterisation approaches. Renewal theory has been proposed as an approach to measure phase singularity (PS) dynamics in AF. We aimed to evaluate the hypothesis that spatial gradients of renewal rate constants in the PV-LA (pulmonary vein-left atrial) junctional region associate with AF ablation outcomes.

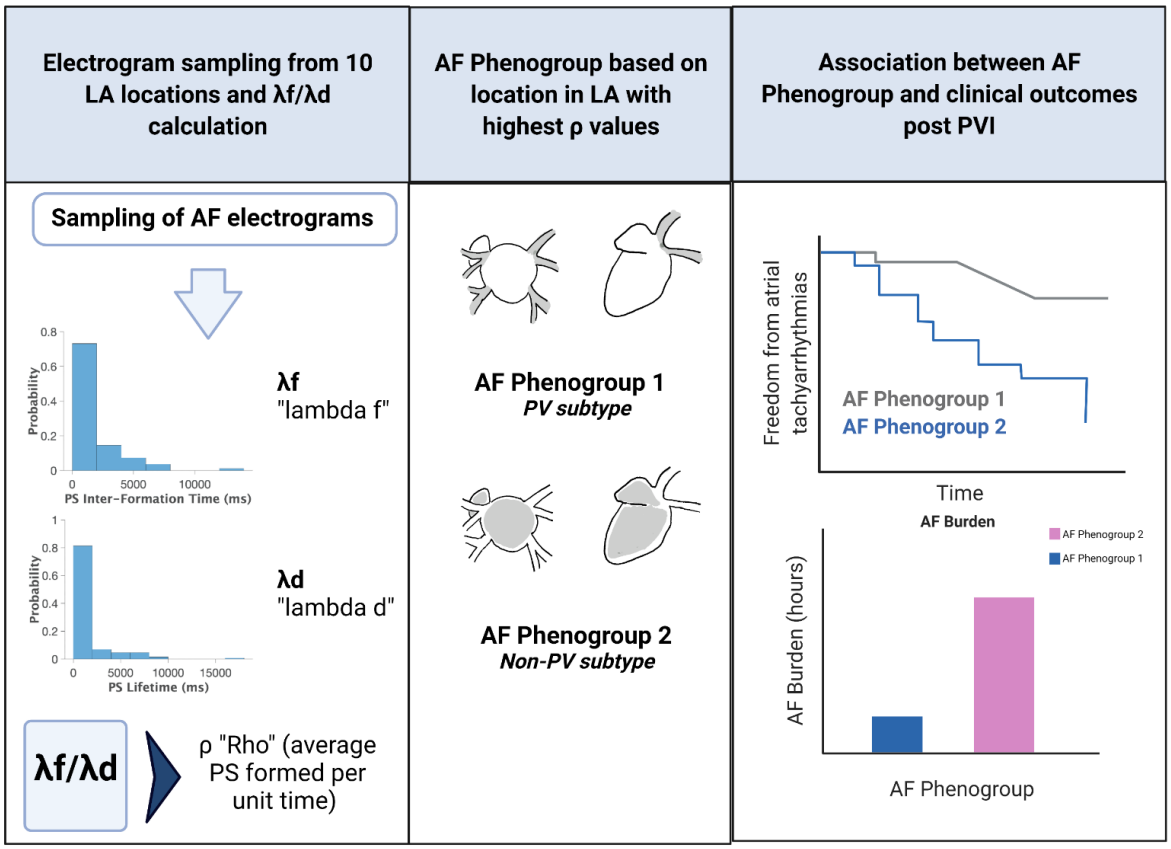
Methods: RENEWAL-AF is a prospective multicentre observational study recruiting paroxysmal and persistent AF ablation patients (ACTRN12619001172190p). One-minute unipolar electrograms were recorded from ten anatomically pre-specified LA locations using a 16-electrode Advisor^{TM} HD-Grid catheter. Rates of phase singularity (PS) formation, λ_f, PS destruction, λ_d, and rho (ρ) values (λ_f / λ_d,) were calculated for each region, and the association with clinical outcomes evaluated. Primary endpoint was defined as freedom from AF/atrial tachyarrhythmia recurrence detected by ECG or AliveCor monitoring, stratified by phenogroups defined by PV-LA renewal rate gradients. Phenogroup 1 (Ph1) was defined as patients with a positive PV-LA renewal gradient, and Phenogroup 2 patients with a negative PV-LA renewal gradient.

Results: N=48 AF patients were recruited (mean age 59.1 ± 9.4 years, 59% persistent AF). Ph1 was associated with lower atrial tachyarrhythmia (AT) recurrences (P=0.047) with a lower AF burden (P=0.016) post ablation. Ph1 patients had a lower CHA_2DS_2-VASC score (P=0.02), and a lower incidence of CVA (P=0.03). No significant association was observed between AF Phenogroup and paroxysmal-persistent AF classification (P=0.68).

Conclusion: Using renewal theory, the presence of spatial ρ gradient between PV-LA enabled definition of a cohort of patients with relatively favourable AF ablation outcomes.

3.2 Central illustration: Figure 3.1: Association between AF Phenogroup and clinical outcomes post PVI-only procedure

Figure 3.1 showing 1) Left panel, sampling of AF electrograms with subsequent calculation of rates of phase singularity (PS) formation (λ_f) and destruction (λ_d) times and rho (ρ) (average PS formed per unit time) calculation 2) Middle panel, classification of AF patients into AF Phenogroups based on the location in the LA with the highest ρ value and 3) Right panel, the significant association between AF Phenogroup with recurrence of atrial tachyarrhythmia and AF burden post PVI-only procedure.



3.3 Introduction

Atrial fibrillation (AF), the most common human arrhythmia, is characterized by aperiodic and non-repetitive electrical activation of the atrium,(60) with the continuous formation and destruction of spiral waves.(16) Clinically, it remains challenging to resolve the pathogenesis of AF in individual patients. To date, two of the principal hypotheses most commonly presented to explain the AF mechanism are: (i) AF occurs via the action of time-translationally stable spiral waves, serving as coherent drivers of fibrillation, with the creation and annihilation of spirals occurring via a secondary process of spiral breakup;(197, 559) or (ii) AF is a form of fully-developed extensive spatiotemporal chaos,(560) with repetitive birth and death of spirals occurring as an autonomous deterministic self-sustaining biological process.(61)

The inconclusive results of the past decade of AF ablation trials of interventions beyond pulmonary vein isolation (PVI),(76, 243) (39) suggests at the current time it is important to remain open to alterative scientific approaches to intra-procedural electrophysiological mapping that could potentially inform decision-making during ablation.(561) Here, we sought to evaluate one such potential approach, namely the possibility that a recently developed theoretical, experimental and clinical approach to AF mapping using renewal theory,(16, 457, 472, 562) could assist electrophysiologic characterisation of AF ablation patients. Renewal theory is a relatively recent quantitative statistical approach which measures the formation and destruction rate of re-entrant circuits in AF. (16, 457, 472, 520, 563, 564) The key idea of the renewal approach to the mapping of AF is that the formation and destruction of spiral waves, tracked by their pivot points known as phase singularities (PS), converge to temporally stable rates, thereby yielding characteristically exponential probability distributions for PS inter-formation and PS lifetimes.(16, 457, 520, 563) By combining these rates, we have shown that a Poisson probability distribution of PS is accurately predicted in multiple systems of AF.(16, 457, 520, 563)

An attractive feature of the renewal theory approach is that repetitive creation and annihilation of unstable spirals observed in AF is a ubiquitous motif in comparably spatiotemporally turbulent physical, (526) chemical,(565) and biological systems throughout nature,(525, 528) providing both a logical scientific rationale for the use of the renewal approach. Despite the diversity of these systems, the population dynamics for spiral waves remarkably show common statistical properties. Specifically, spiral lifetimes in each of these systems has been observed to follow and exponential distribution, and the spiral population distribution follow Poisson distributions. (526-528, 566) (Figure 1) These features are the hallmark of renewal processes. (16, 457, 472, 520) Such distributions of spiral lifetimes have also been observed in AF mapping by others (82, 461, 463, 464) suggesting universality. (520, 563) We have extensively validated the use of renewal theory for fibrillatory dynamic analysis in AF, showing that the rate of formation (λ_f, pronounced as lambda 'f') and destruction (λ_d, pronounced as lambda 'd') of PS converge to temporally stable rates. (16, 457, 520) (Figure 1) We have further validated renewal theory in ventricular fibrillation. (472)

The renewal approach to AF characterization is different to previous approaches to fibrillatory analysis, as it is based on the statistical evaluation of *aggregate* pattern dynamics in AF.(520, 563) In a recent study, we showed that spatial gradients of renewal rate constants could potentially be used to explore inter-atrial electrical connectivity in AF.(562) We showed a positive linear association in renewal constants between anatomically connected regions of the atrium across the inter-atrial association,(562) a result consistent with notion of synchronization that occurs between physically connected contiguous turbulent systems.(567) In this study, we sought to explore a related proposition, namely that similar spatial gradients of renewal rate constants could be important in the pathogenesis of clinical AF. Reasoning that the pulmonary vein (PV) – left atrial (LA) junction has thus far been the critical region in the clinical modulation of AF.(568-570) In this study, we sought to evaluate the hypothesis that that spatial

gradients between the PV and the LA body could be potential determinants of clinical response to PVI-only ablation.

3.4 Methods

Study population

RENEWAL-AF is an ongoing prospective multicentre observational study involving four Australian hospitals. All AF patients with clinical indications for AF ablation and referred for AF ablation were eligible for recruitment (31). This study was approved by the Southern Adelaide Local Health Network Ethics Committee (HREC/19/SAC/292). All patients provided written informed consent. Baseline demographics and transthoracic echocardiogram were obtained pre-procedurally and stored in an electronic database (Redcap, Vanderbilt University, VA).

Electrophysiology study

Electrophysiologic studies were conducted at least five half-lives free of antiarrhythmic drug therapy, whenever feasible, except in patients taking amiodarone. Patients were mapped under spontaneous or induced AF using the Ensite Precision electroanatomic mapping system (Abbott Cardiovascular, Plymouth MN). Electrograms and ECG were recorded at 1000 Hz, and unipolar electrogram filter band pass was set at 0.5-500 Hz. Sequential one-minute recordings of unipolar and bipolar electrograms were obtained using the Advisor^{TM} HD-Grid catheter (16 electrodes in a square grid catheter 13x13mm^2 grid, 3mm interelectrode-spacing, Abbott Cardiovascular, Plymouth MN) from sixteen different intracardiac locations; six RA locations, 1) Superior vena cava (SVC) – RA junction 2) RA appendage 3) RA septal region 4) RA posterior region 5) RA lateral region 6) RA cavotricuspid isthmus region and ten LA locations, 1) Left superior pulmonary vein 2) Left inferior pulmonary vein 3) Right superior pulmonary vein 4) Right inferior pulmonary vein 5) Left high posterior wall 6) Left low posterior wall 7) Left lateral region 8) LA appendage 9) LA anterior region and 10) LA septal region. Stability and contact between catheter and LA endocardium were maintained throughout recordings through visualisation of deformation of the HD-Grid catheter on the electroanatomic map on LA endocardial border and presence of sharp local electrograms on the

tracings (Figure 3). A PVI-only using radiofrequency ablation approach was performed by all operators. Endpoint of entrance and exit block from the pulmonary veins was confirmed post ablation.

Signal processing

Unipolar electrogram signals were exported and processed as described previously (447, 457, 472). Sinusoidal recomposition was applied with the dominant frequency set as the wavelet period and phase computed using the Hilbert transform to construct phase maps (82, 447, 457, 472). In each phase map, phase singularities (PS) were detected and tracked as previously described using a convolution kernel method based on topological charge (447, 457, 472). PS tracking enabled calculation of PS lifetimes and inter-formation times (times between consecutive PS formations), which also enabled construction of PS lifetime and inter-formation time distributions (447, 457, 472). PS distributions were fitted using maximum likelihood fitting to estimate the rate of PS formation (denoted as λ_f) and PS destruction (λ_d) (447, 457, 472).

Follow up

All patients enrolled in RENEWAL-AF received a non-invasive Alivecor mobile phone application (app) post AF ablation to monitor AF burden and time to atrial tachyarrhythmia recurrence (days). This form of follow up to determine arrhythmia recurrence and burden was recently used in a randomised trial of alcohol abstinence in AF patients by Voskoboinik et al and from the CAPLA clinical trial which randomised persistent AF patients to a PVI strategy versus a PVI plus PWI strategy (109, 414)**.** Patients were instructed to transmit twice daily 30 second single lead electrocardiogram recordings from Alivecor monitor regardless of symptoms, for a total duration of six months. Additionally, if they had symptoms of AF, patients were asked to transmit a tracing at AF onset and offset of symptoms, so that an estimate AF duration could be made. Atrial tachyarrhythmia recurrence is defined as atrial tachyarrhythmia lasting for ≥ 30 seconds, while time to atrial tachyarrhythmia recurrence is determined from the Alivecor cardiac

monitor. In patients not on Alivecor cardiac monitor, the first documented atrial tachyarrhythmia recurrence was made using ECG tracings during patient contact in outpatient clinic. All tracings from ECG or Alivecor monitor were reviewed by two cardiologists, blinded to the patient's clinical subgroup classification. At the end of six months, the following clinical endpoints were measured in clinic or via telephone: Recurrence of atrial tachyarrhythmia, AF-related hospitalisation, requirement for cardioversion for AF, need for repeat ablation procedure for atrial tachyarrhythmia and need for intensification of antiarrhythmic therapy, as defined in the Supplementary methods. In patients on Alivecor monitor, total AF burden (hours) was calculated (Supplemental table 3.1 and supplemental table 3.2). Operators and treating physicians were blinded to the AF Phenogroup status of their patients throughout the entirety of study period.

Statistical analysis

Data was reported as the mean (standard deviation, SD) or the median [interquartile range, IQR] for parametric and non-parametric data, respectively. Data normality was checked using the Shapiro Wilk test. Categorical variables were presented as n (%) and differences between groups were examined using the χ^2 test. Continuous variables were analysed using student t test or Wilcoxon-rank sum test, where appropriate. Kaplan Meier curve and log-rank test were used to compare freedom from atrial tachyarrhythmia between clinical subgroups. In univariate and multivariate analysis, recurrence of atrial tachyarrhythmias during follow up period was used as the main outcome variable while known clinical variables (CHA_2DS_2-VASc score, OSA and alcohol intake) and echocardiographic parameters (LA volume index and LV dysfunction, defined as LV ejection fraction<50%) known to predispose to AF were used as the input variables. Results were reported as regression slope (β) and level of significance. Statistical analysis was performed using STATA version 15.1 with the level of significance set for a two-tailed α at P=0.05.

Endpoint Definitions

The primary endpoint was defined as freedom from any documented recurrence of atrial fibrillation or sustained atrial tachyarrhythmia lasting >30 seconds, detected by ECG or AliveCor monitoring. The secondary endpoint was the burden of AF. The burden of AF was defined as the percentage of the time spent in AF, defined by the burden of AliveCor tracings showing evidence of AF as previously described by Voskoboinik et al (414).

3.5 Results

Baseline and procedural characteristics

A total of n=48 patients were recruited in this study. A consort diagram showing the flow of recruitment into the study is shown in Supplemental Figure 1. Mean age (years) of the total cohort was 59.1 ± 9.4, 28.5% female, mean BMI (kg/m^2) was 31.2 ± 4.4 while the mean CHA_2DS_2-VASc score was 1.9 ± 1.6 (Table 3.1). The clinical indications for AF ablation in this cohort were AF symptoms refractory to antiarrhythmic drug therapy, n=21(51%), followed by LV systolic dysfunction, n=14(34%) and antiarrhythmic drug intolerance, n=6(15%). N=7 patients were excluded from final analysis due to inability to induce AF during index procedure (n=3), hemodynamic instability during procedure (n=2), frequent AF termination (n=1) and atypical atrial flutter (n=1).

AF Phenogroup classification

The current clinical practice of classification of AF patients into paroxysmal or persistent forms has been used as a guide for clinicians to dictate decisions for therapy and for patient's recruitment into key AF trials. However, the paroxysmal persistent classification scheme that dominates clinical practice may not be able to capture and quantify the full extent of clinical and physiological AF heterogeneity. Recent studies have shown a significant discrepancy between this clinical classification of AF with its actual

temporal persistence (32-34). In addition, other studies have also shown a limited predictive ability of this pAF-persAF classification for adverse clinical outcomes in AF patients (35, 36). Whilst convenience is an attractive factor for ongoing use of pAF-persAF classification in clinical practice, it remains insufficient by itself to define the subgroup of patients with persistent AF, who are responsive to PVI-only based ablationIn a recent study, we identified that spatial gradients of renewal rate constants were enabled the statistical evaluation of inter-atrial connectivity during sustained AF.(562) This result was in line with known features of the synchronization of connected chaotic systems.(567) Here, building on the known importance of the PV–LA junction region in AF ablation, we reasoned that spatial gradients of renewal rate constants could potentially be key determinants of AF ablation outcomes.

In this study, we characterised AF patients based on the location of the highest averaged PS formed per unit time, or rho value, ie, AF Phenogroup 1 patients would have the highest rho values in the pulmonary veins. Mechanistically, we hypothesise that this represents clustering or increased PS density in the pulmonary veins. Previous studies have shown a predilection of re-entrant circuits to drift to atrial regions with prolonged APD, areas with ionic heterogeneities or areas with reduced excitability (571, 572). Specifically, an atrial region of interest is around the LA-pulmonary vein junction where previous studies have shown the role of a heterogenous distribution of transmembrane currents and the presence of excitable gradient in attraction re-entrant circuits to this region (237). Structurally, this may be attributed by the complex architecture of myocardial fibre orientation and fibrotic remodelling observed in canine and human models of AF (573, 574).

To test this hypothesis, we examined clinical outcomes of AF ablation in two Phenogroups defined by differences spatial gradients of renewal rate constants at the PV-LA junction (Central illustration: Figure 3.1). We defined Phenogroup 1 was defined as patients with a positive gradient of λ_f/λ_d between the pulmonary veins and left atrium. Phenogroup 2 was defined as patients with a negative gradient of λ_f/λ_d

between the pulmonary veins and the left atrium. Case examples illustrating Phenogroup classification are presented in Figure 2.

When divided into Phenogroup 1 and Phenogroup 2 based on the location of highest λ_f/λ_d values, n=16 (44%) of patients were in Phenogroup 1. CHA_2DS_2-VASc score was lower in Phenogroup 1 compared to Phenogroup 2 (1.2 ± 1.1 vs 2.3 ± 1.6, P=0.02) (Table 3.1). (Table 1). No significant differences were observed in the procedural time (skin-to-skin, minutes) (P=0.57), fluoroscopy time (minutes) (P=0.71) and radiofrequency ablation time (minutes) (P=0.73) between both groups (Supplemental table 3.3).

Clinical Outcomes of AF ablation according to AF Phenogroup Classification

In this section, we present the clinical outcomes of PVI according to AF Phenogroup classification. In section 1, we show clinical case examples of AF patients falling into the different AF Phenogroups. In section 2, we present overall summary data for clinical outcomes. Four case examples of spatial distribution of rho and corresponding AF Phenogroup are as presented below:

Section 1

Four clinical examples of patients in different AF Phenogroups are as presented in Figure 3.2. On the left panel, patients in AF Phenogroup 1 and on the right panel, patients in AF Phenogroup 2.

Patient 1 (Figure 3.2, top left panel) was 61-year-old male with BMI of 30 and CHA_2DS_2-VASC of 1. The patient has had pAF for seven years prior to PVI and was on flecainide for rhythm control. The patient was referred for PVI due to increasing frequency of symptomatic paroxysmal episodes of AF. Echocardiographic findings included LVEF of 44% and LAVi 35 ml/m^2. The patient was classified into AF Phenogroup 1 because of the highest λ_f/λ_d values in the right superior pulmonary vein. The patient had no recurrence of AF after six months follow up, with no AF documented on Alivecor monitor.

Patient 2 (Figure 3.2, top right panel) was 51-year-old male with BMI of 37 and CHA_2DS_2-VASC of 5. The patient had persAF diagnosed 7 years prior to PVI and was on amiodarone for rhythm control**.** Echocardiographic findings included LVEF of 44 % and LAVi 62 ml/m^2. The patient was classified into Phenogroup 2 because of the highest λ_f/λ_d values in the LA lateral wall. After PVI, the patient had AF recurrence 2 weeks post AF ablation, with total AF burden of 504 hours further complicated by the need for increase in amiodarone dose and is currently planned for elective electrical cardioversion.

Patient 3 (Figure 3.2, bottom left panel) was 60-year-old male with BMI of 30 and CHA_2DS_2-VASC of 1. The patient had been in persAF for 24 months prior to PVI and was on amiodarone for rhythm control.

Echocardiographic findings included LVEF of 32% and LAVi 57 ml/m^2. The patient was classified into AF Phenogroup 1 because of the highest λ_f/λ_d values in the left superior pulmonary vein. The patient had no recurrence of AF after six months follow up, with no AF documented on Alivecor monitor.

Patient 4 (Figure 3.2, bottom right panel) was 59-year-old female with BMI of 26 and CHA_2DS_2-VASC of 2. The patient had pAF diagnosed 53 months prior to PVI and was on sotalol for rhythm control**.** Echocardiographic findings included LVEF of 59% and LAVi 44 ml/m^2. The patient was classified into AF Phenogroup 2 because of the highest λ_f/λ_d values in the left atrial appendage. After PVI, the patient had AF recurrence 72 hours post AF ablation further complicated by need for intensification of antiarrhythmic therapy to amiodarone, AF-related hospitalisation, need for cardioversion and subsequent requirement for re-do AF ablation procedure. No AF burden data was available for this patient.

Section 2

Clinical Outcomes of AF ablation according to AF Phenogroup Classification

AT/AF recurrence was lower in AF Phenogroup 1 compared to Phenogroup 2 (n=6[37.5%] versus n=16[69.6%], P=0.047). In n=30 patients (n=12[75%] Phenogroup 1, n=18[72%] Phenogroup 2), AF burden (hours) was significantly lower in Phenogroup 1, when compared to Phenogroup 2 (median of 0 hours [IQR: 0 – 8 hours versus 38 hours [IQR: 0 – 240 hours], respectively, P=0.028) (Table 2). A significantly longer time to AT/AF recurrence was also observed in Phenogroup 1 compared to Phenogroup 2 after six-months follow up (HR 3.74, CI 1.4-11.2, P=0.007) (Figure 3.3).

No relationship was observed between AF Phenogroup versus pAF-persAF classification (P=0.68). When clinical outcomes from PVI-only ablation were analysed according to patients pAF-persAF classification, this was not predictive of clinical response to PVI measured by AF burden (P=0.58) and AF recurrence

(P=0.54) (Supplemental table 5). Time to AT/AF recurrence was not significantly different comparing pAF versus persAF groups (HR 0.84, CI 0.35-2.0, P=0.64) (Figure 3.3).

Predictors of AT/AF recurrence post ablation

In univariate binary logistic regression analysis using atrial tachyarrhythmia recurrence as the dependent variable, AF Phenogroup classification was the only significant predictor of this adverse clinical outcome post PVI (β +0.33, 95% CI 0.02 0.64, P=0.036) (Table 3). Additionally, in multivariate regression analysis, AF Phenogroup remained an independent predictor of atrial tachyarrhythmia recurrence post PVI-only AF ablation (β +0.33, 95% CI 0.002 0.66, P=0.05) (Table 3).

3.6 Discussion

RENEWAL-AF is a proof-of-concept, prospective multicenter study using renewal theory as an electrophysiological-based approach to determine responsiveness to PVI. Using renewal theory, we identified a cohort of AF patients who had favorable clinical outcomes post PVI. Specifically, AF Phenogroup 1 (pulmonary vein subtype) was associated with a lower atrial tachyarrhythmia recurrence and lower AF burden compared to patients in AF Phenogroup 2 (LA body subtype). An interesting finding was that the renewal theory based Phenogroup classification diverged from pAF-persAF AF pattern classification. These findings may have the potential to complement currently used risk stratification schemes for AF patients, potentially enabling a tailored ablation strategy for each AF Phenogroup and improve patient selection for PVI vs PVI plus strategies in future AF clinical trials.

Insights from computational models of AF: AF Phenogroup 1

Using atrial bilayer models and fibrosis data obtained from LGE-CMR from persistent AF patients, Saha et al observed a preferential clustering of PS around regions with high action potential gradient density around the ostia of the inferior pulmonary veins in the absence of fibrosis and 2) clustering of PS around borders and within fibrotic zones, in atrial models with fibrosis (236). Furthermore, another study using

computational models of atrial models derived from MRI data observed that the presence of fibrosis in the PV results in high clustering of PS within the PV, with a higher PS density and increasing the likelihood AF termination post simulated PVI-only procedure (575). Importantly, Roney et al also highlighted the role of pulmonary veins not only with initiation of arrythmia (slower conduction velocity around the LA-PV junction), but also with AF maintenance (through PV fibrosis resulting in re-entry, rotor meandering to fibrotic regions and stabilisation of re-entrant circuits in PV regions with extensive fibrosis) (575). Findings from RENEWAL-AF is concordant with these findings from Roney et al, in which patients in AF Phenotype 1, with the highest rho value in the pulmonary veins, defined as the average PS formed per unit time, showed a significantly lower rate of recurrence from AF, with a lower AF burden post a PVI-only procedure.

Insights from computational studies and CMR-LGE data: AF Phenogroup 2

Conversely, in AF Phenogroup 2 patients, highest rho values were observed in the atrial regions within the LA body. This was associated with both evidence of LA structural remodelling and poorer clinical outcomes post a PVI-only procedure. Formation and progression of atrial fibrosis plays a crucial role in AF initiation and persistence (14). Computational studies have shown predilection of PS to fibrotic borders, resulting in anchoring of PS to these regions and formation of new wavebreaks and PS, sustaining AF (225, 236, 576). Not surprisingly, using simulated computational models of AF, Roney et al also showed a lower rate of AF termination after a PVI-only approach when PS clusters were observed in the LA body, when compared to PS clusters in the pulmonary veins (575). In human studies of persistent AF, using a non-invasive electrocardiographic imaging consisting of 252 chest electrodes for localisation of re-entrant activities and CMR-LGE fibrosis localisation and quantification, Cochet et al showed clustering of the re-entrant circuits around the fibrotic borders within the LA body, with the number of PS increasing with burden of fibrosis and AF duration (234).

Clinically, it would be reasonable to hypothesise that ablation of these atrial fibrotic regions would be beneficial given the attraction of PS to the borders of these regions. However, we observed equivocal results from the ALICIA trial and DECAAF 2 trials, a randomised study targeting fibrotic regions in the LA, in addition to PVI, when compared to PVI alone (243, 297). It is crucial to highlight that other factors besides presence and burden of fibrosis, including the distribution and patterns of fibrosis (225, 577, 578), type of fibrotic cells (233) and regional changes to both the action potential duration and conduction velocity (235) which can modulate attraction of PS to these regions. AF Phenogroup classification overcomes the assumption of increased PS density around fibrotic borders acting as "drivers", by a direct statistical analysis of the PS density using renewal theory, a branch of probabilistic theory in mathematics.

Association between AF Phenogroup with patient demographics

Higher CHA_2DS_2-VAsC scores has been linked to an adverse clinical AF phenotype and is also associated with enlarged LA volume, a known marker of adverse LA structural phenotype which is an important predictor of poor clinical outcomes post AF ablation (579-581). However, an adverse electrophysiological phenotype for AF remains poorly defined. In our study, we observed significant relationships between both higher CHA_2DS_2-VAsC scores and enlarged LA volume with AF Phenogroup 2, where a higher ρ values were seen within the LA body. This finding is consistent with contemporary mechanistic understanding of AF progression, where there is a shift from PV-based triggers in the early form to a more advanced phenotype, with adverse structural and electrical remodelling in the LA body (310). We hypothesise that renewal-theory based assessment of a patients fibrillatory dynamics could potentially be used to provide an overview of a patients' cumulative underlying electrical and structural remodelling in the LA. Additionally, the renewal approach may help to define an adverse AF electrophysiologic phenotype, reflecting progression of a patients' fibrillatory process. This could be clinically important to dictate treatment strategy individualised for a patient's AF Phenogroup.

AF Phenogroup: Clinical implications

From a clinical perspective, there is growing interest in defining a potential subgroup of persistent AF patients that could be responsive to PVI only ablation. An earlier meta-analysis has suggested that a subset of persistent AF patients with minimal echocardiographic evidence of structural heart disease (studies involving predominantly persistent AF patients with mild LA dilatation and normal LV systolic function) who had a single procedure arrythmia free survival of 66.7% after a PVI-only approach, similar to clinical response observed in paroxysmal AF patients post a PVI-only approach (15, 582). In addition, two recent studies have identified pharmacologic-responsiveness to intra-procedural cardioversion as a potential predictor of PVI-only based ablation efficacy. Okawa et al showed improved clinical outcomes with PVI-only ablation in patients responsive to pharmacological cardioversion with Class IV calcium-channel blocker bepridil (126). Similarly, He et al. suggested intra-procedural ibutilide cardioversion was a predictor of PVI-only effectiveness in persAF cohort (583). RENEWAL-AF adds to contemporary understanding of this issue on three levels: (i) it offers a potential mechanistic explanation for the phenomenon of PVI-responsiveness; (ii) it provides a way direct way to measure this physiologically during the ablation procedure; (iii) the renewal theory paradigm postulated in the RENEWAL-AF study provides detailed electrophysiological insight into the mechanisms sustaining AF that could be used as a generic foundation for developing new AF ablation strategies. Specifically, with the advent of pulsed field ablation catheters (PFA), anatomical characterization of renewal rate constants throughout the atrium could potentially allow new types of physiologically directed ablation procedures based on patient-specific atrial compartmentalization.

The strength in classification of AF using the renewal theory lies in the fact that it relies on fundamental electrophysiological properties of the fibrillatory process. It was Garrey in 1914 who noted that AF was sustained by 'shifting circuits of multiple complexity (584).' Unstable re-entry has subsequently been a consistent finding in the field (62, 75, 523). The renewal theory approach relies on this stable statistical

property of the fibrillatory process. We have previously shown that by plotting the lifetime and arrival times of unstable re-entry in computational, animal and human models of AF, a characteristic exponential curve is consistently observed in our own data, and that others (82, 447, 461, 463, 472, 481). Importantly, we have shown that these rate constants are temporally stable (447). We have also shown that these rate constants scale with area under observation, but that the renewal equations themselves are scale invariant under scale transformation (457). More recently, Dharmaprani et al demonstrated the utility of renewal theory to analyse and accurately predict PS and wavefront population distribution from human ventricular fibrillation epicardial sock recordings in human ventricular fibrillation (472), In response to this investigation, questions regarding the clinical utility of the renewal approach were recently raised (585). The RENEWAL-AF study consolidates these earlier mechanistic findings and further demonstrates the clinical utility of renewal theory in AF, by linking patient's baseline characteristics, AF-related atrial structural remodelling and clinical outcomes post AF ablation with λ_f/λ_d, derived from renewal theory-based analysis of fibrillatory dynamics. While earlier hypotheses of AF persistence have been made based on a qualitative or observational approach (multiple wavelet hypothesis versus mother rotor hypothesis), this new conceptual paradigm of AF is based on fundamental statistical properties of the fibrillatory process observable using electrophysiologic recordings in the electrophysiology lab.

Clinical Implications and Future Directions

The findings of RENEWAL-AF at the current time would be considered hypothesis-generating, but potentially show a promising path forward over conventional approaches to AF mapping. We would argue that the findings from RENEWAL-AF should ideally be confirmed in a larger prospective study, using higher density electroanatomic maps and sampling from a larger number and area of locations within the atrial chamber to improve sampling coverage. At the current time, several future applications of the renewal statistical approach are underway. At present, we are actively developing real-time measurement of the renewal rate constants λ_f & λ_d. Live measurement of the renewal rate constants could allow real-time

modulation of λ_f/λ_d in AF patients undergoing ablation, a potentially new way of performing the ablation. Secondly, we are also developing new tools to assess λ_f & λ_d non-invasively from ECGi and ECG recordings in AF. This could enable use of these fundamental rate constants in AF classification and patient-selection for ablation.

The findings of RENEWAL-AF may also have implications for the development of new approaches to the clinical classification of AF based on the physiological dynamics of the fibrillatory process. The favourable clinical outcomes associated with PVI in Phenogroup 1 over Phenogroup 2 are consistent with a notion that the fibrillatory process may evolve from a pulmonary vein based phenomenon towards to a more spatially generalised dynamics affecting the body of the atria. Concordant with this notion is that contemporary risk factors for AF progression, such as CHA_2DS_2-VaSC score, and LA size markers were correlated with Phenogroup 2 classification. On the other hand, time spent in AF as determined by AF pattern classification only partially overlapped with the Phenogroup classification. It is possible that the AF Phenogroup classification developed here in the context of AF ablation patients, could have implications for understanding the mechanistic progression of AF in non-ablation cohorts.

Limitations

Potential limitations of study findings include the enrolment of a relatively small number of patients. However, the renewal theory approach used for fibrillatory dynamic analysis is a robust technique that has been validated not only in human atrial and ventricular fibrillation but also in multiple physical systems in nature including in biology (525, 528), physics (526) and chemistry (527). Secondly, the duration of follow up for these patients is relatively short. However, previous studies have shown, early AF recurrences as an important predictor of adverse clinical outcomes post ablation, including late AF recurrences and need for re-do ablation for AF patients (586, 587). Thirdly, while phase mapping is not universally accepted as a tool to study AF fibrillatory dynamics (558), PS dynamic analysis has been

performed widely not only in cardiac fibrillation, as well as in other comparable turbulent spiral-wave systems throughout nature (425, 525-528, 588).

3.7 Conclusion

Renewal theory approach provides a useful signal-based electrophysiological approach to the assessment of AF fibrillatory dynamics, linked to underlying AF-related clinical risk factors and left atrial structural remodelling which identifies a cohort of AF patients who had improved clinical outcomes post PVI-only procedure. Mechanistically, renewal theory suggest that AF is maintained by continuous regeneration of PS, a spectrum of PS behaviour consisting predominantly of transient re-entrant circuits but also longer lasting PS, bridging two current hypothesis of AF persistence, namely the mother rotor and multiple wavelet hypothesis. Characterisation of PVI-only responders in AF patients will assist in improved patient stratification for a PVI-only strategy, prevent arrhythmogenic effect of unnecessary additional substrate modification and identify a cohort of AF patients who might benefit from additional ablation strategies beyond PVI.

3.8 Tables

Table 3.1: Baseline characteristics of patients in all patients, and in patients classified by AF Phenogroup

Baseline Demographics	All patients (n=41)	AF Phenogroup 1(n=16)	AF Phenogroup 2 (n=25)	P-value
Age (years)	59.1 (9.4)	56.3 ± 10.3	60.8 ± 8.6	0.13
BMI (kg/m^2)	31.2 (4.4)	31.4 ± 4.6	31.1 ± 4.4	0.79
Sex, female [%]	12 [28.5]	5 [31.3]	7 [28]	0.8
Diabetes mellitus [%]	3 [7]	1 [6.3]	2 [8]	0.83
Hypertension [%]	17 [40.5]	5 [31.2]	12 [48]	0.3
Vascular disease [%]	8 [19.5]	4 [25]	4 [16]	0.48
Hyperlipidemia [%]	13 [31]	6 [37.5]	7 [28]	0.52
OSA [%]	14 [34]	5 [31.3]	9 [36]	0.75
Heart failure [%]	17 [41.5]	6 [37.5]	11 [44]	0.68
CVA [%]	6 [14]	0 [0]	6 [24]	0.03
Smoking history [%]	10 [23.8]	3 [18.8]	7 [28]	0.5
Alcohol intake [%]	27 [64.3]	10 [62.5]	17 [68]	0.72
Alcohol standard drinks/week	5.7 (11.7)	4.1 (5.1)	6.7 (14.5)	0.5
CHA2DS2-VASc score	1.9 (1.5)	1.2 ± 1.1	2.3 ± 1.6	0.02
Paroxysmal AF [%]	17 [41]	6 [37.5]	11 [44]	0.68
Antiarrhythmic use				
Sotalol [%]	10 [23.8]	3 [18.8]	7 [28]	0.5
Amiodarone [%]	15 [36.6]	5 [31.3]	10 [40]	0.57
Flecainide [%]	10 [23.8]	5 [31]	5 [20]	0.41

Values are given as mean (standard deviation) or n [%]. BMI, Body mass index; LV, left ventricular; EF, ejection fraction; OSA, obstructive sleep apnea; CVA, cerebrovascular accident; LA, left atrium.

Table 3.2: Clinical outcomes post PVI-only procedure, by AF Phenogroup classification.

Clinical outcomes measured	AF Phenogroup 1 (n=15)	AF Phenogroup 2 (n=24)	P-value
Atrial tachyarrhythmia recurrence, n [%]	5 [33]	16 [66.7]	0.042
Atrial tachyarrhythmia burden on Alivecor (hours)	0 (0-8)	38 (0-240)	0.028
Escalation in antiarrhythmic therapy	2 [13.3]	6 [25]	0.38
Electrical cardioversion	2 [13.3]	2 [8.3]	0.62
Atrial fibrillation, atrial flutter and/or atrial tachycardia ablation	1 [6.7]	4 [16.7]	0.34
AF-related hospitalisation	4 [27]	5 [20.8]	0.67

Data presented as n [%], median (IQR) or mean ± standard deviation. AF recurrence is defined as AF documented on 12-lead surface ECG or single lead Alivecor cardiac monitor.

Table 3.3: Association between AF pattern and clinical outcomes

Clinical outcomes measured.	Paroxysmal AF (n=15)	Persistent AF (n=24)	P-value
Atrial tachyarrhythmia recurrence, n[%]	9 [60]	12 [50]	0.54
Atrial tachyarrhythmia burden on Alivecor (hours)	24 (0-108)	0.5 (0-142)	0.58
Escalation in antiarrhythmic therapy	4 [26.7]	4 [16.7]	0.45
Electrical cardioversion	2 [13.3]	2 [8.3]	0.62
Atrial fibrillation, atrial flutter and/or atrial tachycardia ablation	3 [20]	2 [8.3]	0.29
AF-related hospitalisation	6 [37.5]	3 [12.5]	0.05

Data presented as mean ± standard deviation, median (IQR) or n [%].

Table 3.4: Univariate and multivariate predictors of AT/AF recurrence post ablation

Variable	**Univariate model β, 95% CI**	**P-value**	**Multivariate model β, 95% CI**	**P-value**
Persistent AF	-0.1 (-0.43, 0.23)	0.55		
OSA	-0.23 (-0.56, 0.1)	0.17		
Alcohol intake	-0.27 (-0.6, 0.05)	0.1	-0.28 (-0.61, 0.04)	0.09
CHA_2DS_2-VASc score	+0.08 (-0.02, 0.18)	0.13	+0.02 (-0.09, 0.13)	0.71
LA volume index (ml/m^2)	+0.014 (-0.005, 0.033)	0.14		
LV ejection fraction (%)	-0.007 (-0.02, 0.01)	0.37		
AF Phenogroup	+0.33 (0.02, 0.65)	0.036	+0.33 (-0.003, 0.66)	0.05

Data presented as β coefficient, 95% confidence interval and their associated P-value.

Supplemental table 3.1: Alivecor patient recruitment and compliance to tracings

Parameter	**AF Phenogroup 1 (n=16)**	**AF Phenogroup 2 (n=25)**
Alivecor offered	16 (100%)	25 (100%)
Alivecor refused by patients	4	7
Total number of patients on Alivecor	12	18
Compliance with tracings	86%	84%

Supplementary table 6 showing Alivecor cardiac monitor uptake and tracing compliance. Data presented as n (%). Compliance to Alivecor cardiac monitor was measured by percentage of tracings transmitted over the expected number of tracings.

Supplemental table 3.2: Procedural characteristics of AF ablation, by AF Phenogroup

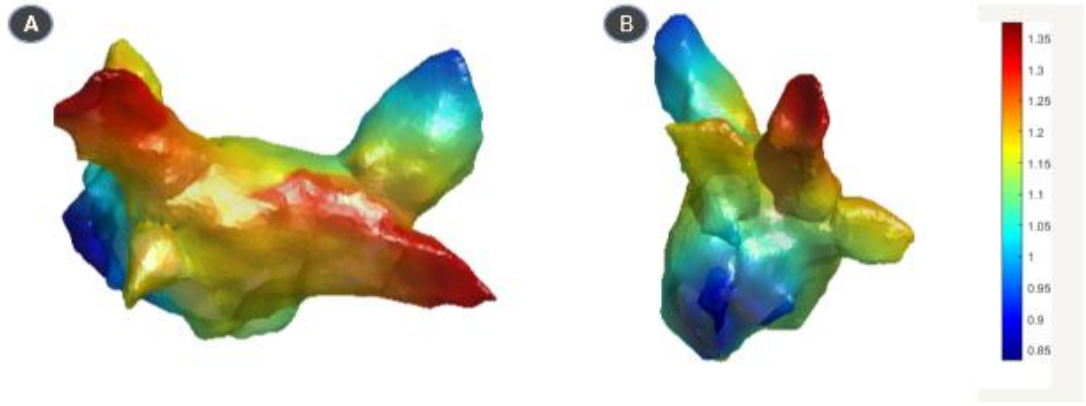
Parameter	AF Phenogroup 1 (n=16)	AF Phenogroup 2 (n=25)	P-value
Procedural time (skin-to-skin) (minutes)	180.8 ± 76.7	193.7 ± 66.3	0.57
Average fluoroscopy time per patient (minutes)	32.3 ± 23.7	34.4 ± 11.1	0.71
Average radiofrequency time per patient (minutes)	1540 ± 761	1620 ± 621.5	0.73

Data presented as mean ± standard deviation.

3.9 Figures and supplemental figures

Figure 3.2: Example of patients in different AF Phenogroups. Demographic, echocardiographic, and clinical outcomes data are presented in each panel. Top panel, AF Phenogroup 1 patients. Bottom panel, AF Phenogroup 2 patients.

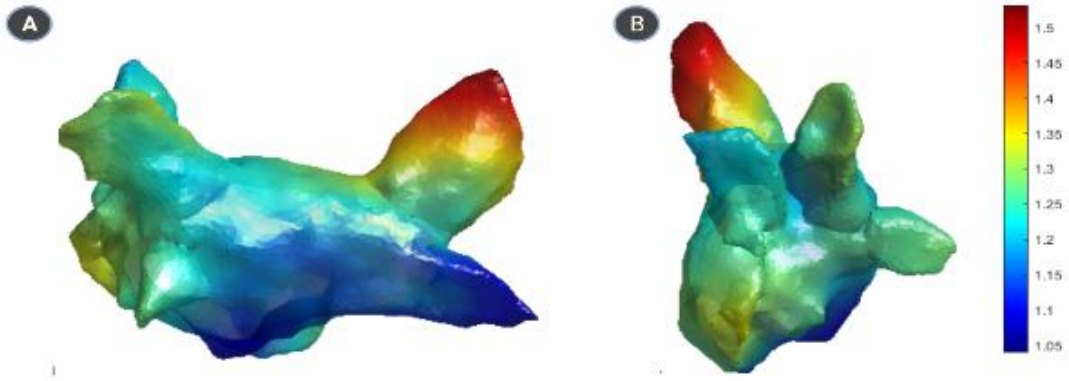
AF PHENOGROUP 1



C
Age : 60
BMI : 30
CHADS VASC score : 1
Persistent AF diagnosed 24 months prior to PVI
Antiarrhythmic therapy: Amiodarone

D
LV function: LVEF 32%
LA size : 57 ml/m^2
AF Phenogroup 1 : Highest λf/λd in the LSPV (ρ=1.33) followed by RIPV (ρ=1.28)

E
No AF recurrence at 6 months follow up
No AF detected on Alivecor monitor

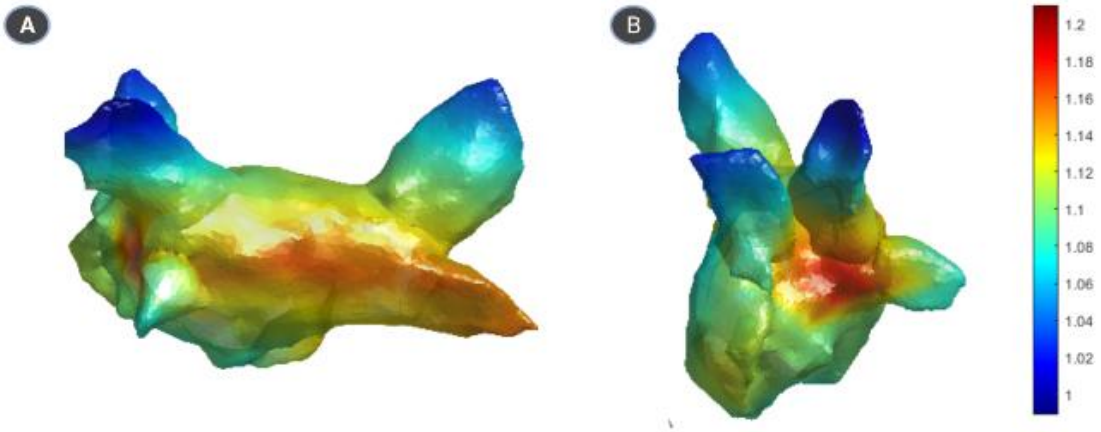


C
Age : 61
BMI : 30
CHADS VASC score : 2
Paroxysmal AF diagnosed 7 years prior to PVI
Antiarrhythmic therapy: Flecainide

D
LV function: LVEF 44%
LA size : 35 ml/m^2
AF Phenogroup 1 : Highest λf/λd in the right superior pulmonary vein

E
No recurrence of AF at 6 months follow up
No AF detected on Alivecor monitor

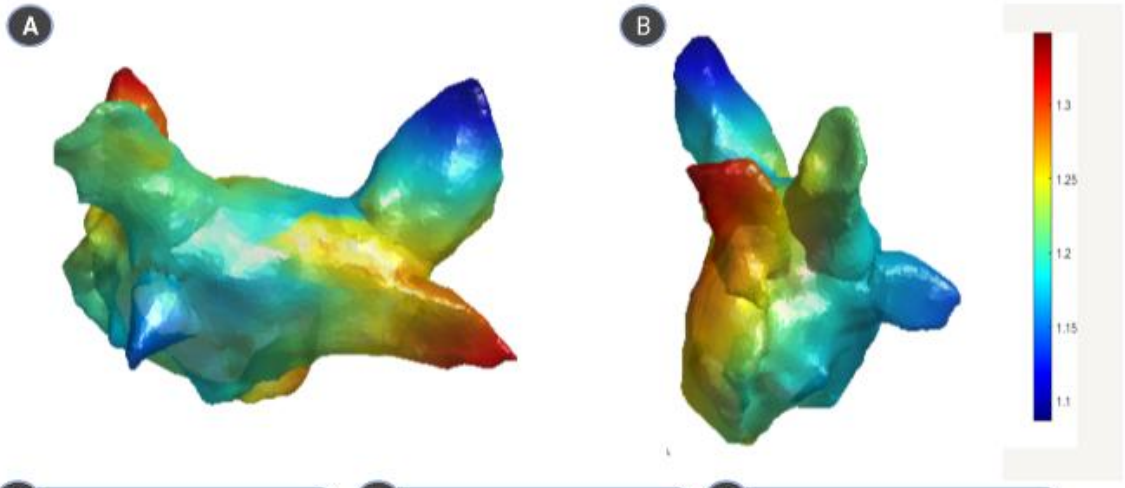
AF PHENOGROUP 2



C
Age : 51
BMI : 37
CHADS VASC score : 5
Persistent AF diagnosed 7 years prior to PVI
Antiarrhythmic therapy: Amiodarone

D
LV function: LVEF 44%
LA size : 62 ml/m^2
AF Phenogroup 2 : Highest λf/λd in the LA lateral wall

E
AF recurrence 2 weeks post PVI
AF burden : 504 hours
Need for incremental dose of amiodarone and planned for elective electrical cardioversion



C
Age : 59
BMI : 26
CHADS VASC score : 2
Paroxysmal AF diagnosed 53 months prior to PVI
Antiarrhythmic therapy: Sotalol

D
LV function: LVEF 59%
LA size : 44 ml/m^2
AF Phenogroup 2 : Highest λf/λd in the LAA (ρ=1.32) followed by RIPV

E
AF recurrence 72 hours post PVI
Intensification of antiarrhythmic therapy
AF-related hospitalisation
Re-do AF ablation procedure

Figure 3.3: Clinical outcomes of PVI-only procedure, comparing AF Phenogroup and paroxysmal-persistent AF classification.

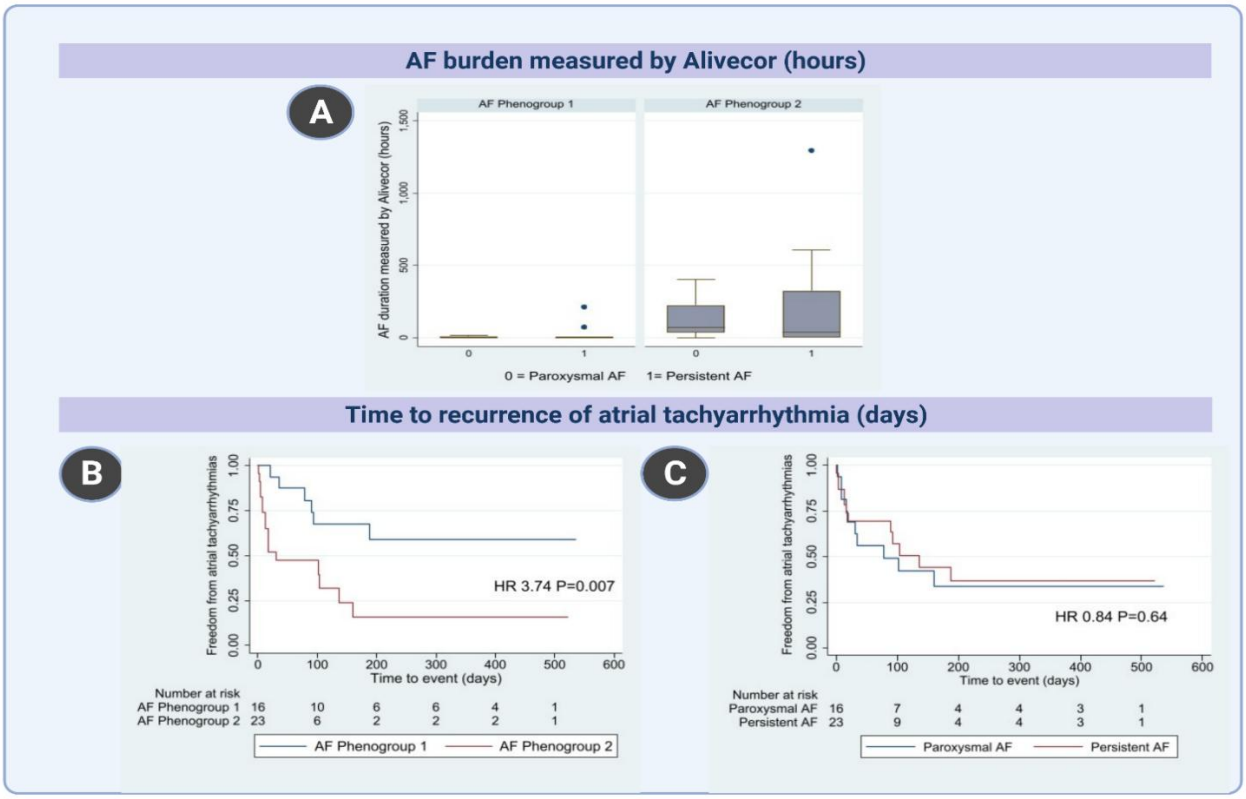
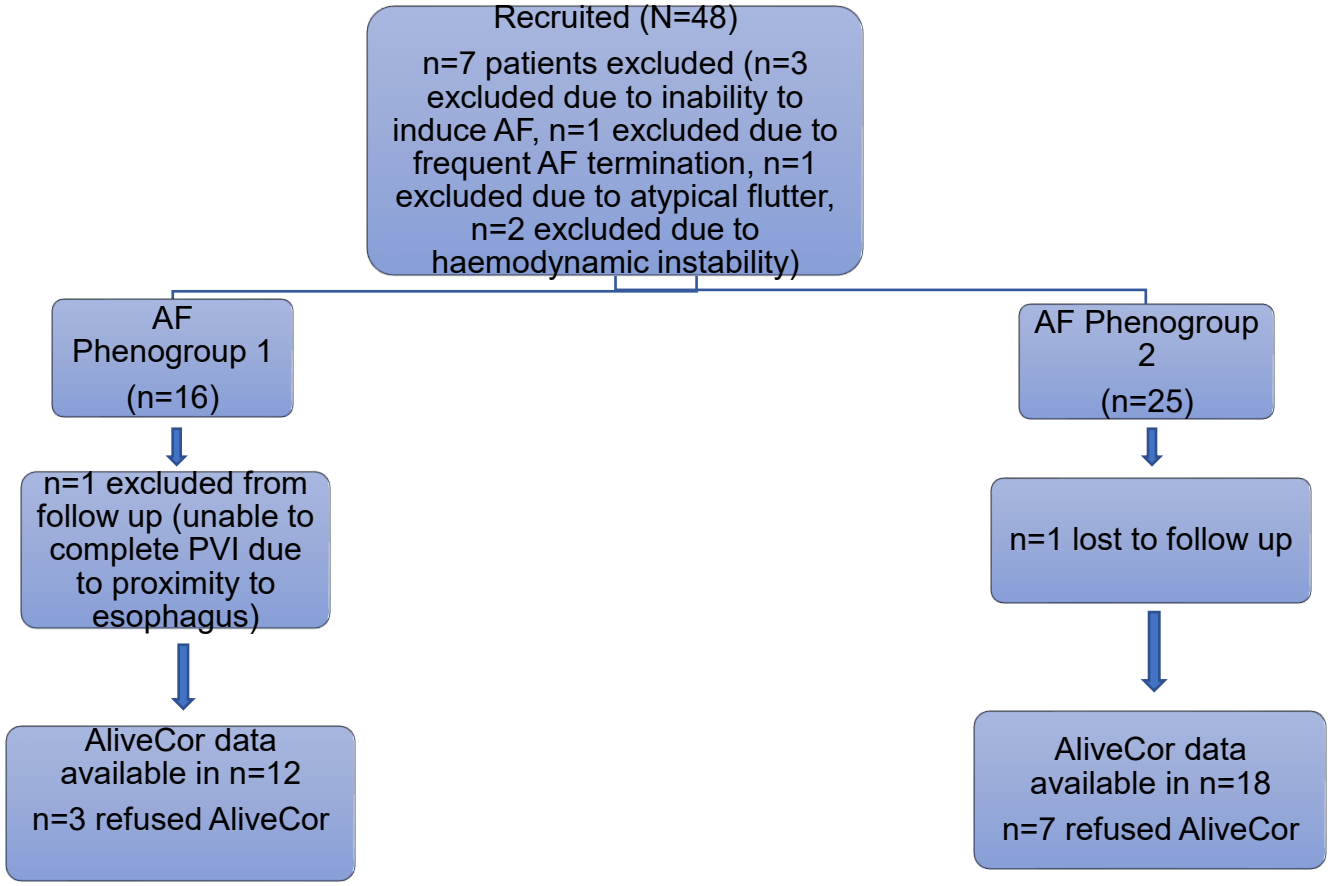


Figure 3.3 showing in A) AF burden measured by Alivecor (hours), by box-plot method comparing AF Phenogroup and paroxysmal-persistent classification (median of 0 hours [IQR: 0 – 8 hours versus 38 hours [IQR: 0 – 240 hours], respectively, P=0.028). B) Kaplan Meier curves showing survival free time from atrial tachyarrhythmias, comparing AF Phenogroup 1 and Phenogroup 2. Significantly longer time to recurrence of atrial tachyarrhythmias was observed in Phenogroup 1 compared to Phenogroup 2 (HR 3.74, CI 1.4-11.2, P=0.007). C) Kaplan Meier curves showing no difference in survival free time from atrial tachyarrhythmias between paroxysmal versus persistent AF patients (P=0.54).

Supplemental Figures

Supplemental Figure 1: Patient recruitment and follow up in RENEWAL-AF



Methods Supplemental Material 1

Follow up

An increasingly utilised method to assess AF control is by the measurement of AF burden. A sub-study from the STAR-AF 2 trial showed that a greater reduction in AF burden translated to a significantly improved quality of life (589). In patients post AF-ablation, AF burden has been used as a surrogate to assess efficacy of different strategies of catheter ablation (590). More recently, Voskoboinik et al also utilised AF burden, measured twice daily using the AliveCor monitor to measure the influence of alcohol abstinence on AF (414). The method proposed by Voskoboinik et al laid the foundation for the approach used to measure AF burden in RENEWAL-AF. More recently, a similar approach to estimate recurrence of AF and to quantify AF burden post AF ablation using a hand held Alivecor monitor was described in the CAPLA trial (109).

AF burden was calculated as the time in atrial fibrillation (hours) after a six-month follow up period, in patients who received and consented to the AliveCor monitor.

AF recurrence was calculated as the time from the day of AF ablation (days) until the day of AF detection either by AliveCor cardiac monitor or the first date of AF documentation on surface ECG in the outpatient's clinic.

Recurrence of AF on AliveCor monitor was defined as at least thirty seconds of AF documented on single lead AliveCor cardiac tracing.

Intensification of antiarrhythmic therapy was defined as post procedural increment in the dose of patient's current antiarrhythmic therapy, compared to pre-ablation or the need to change therapy from any antiarrhythmic (non-amiodarone) to amiodarone.

In patients who received Alivecor cardiac monitor, they were instructed to transmit twice daily 30-second single lead ECG tracing to investigators.

- In patients who developed AF symptoms, they were instructed to transmit an ECG tracing at onset of the symptoms and at offset of symptoms, so an estimated AF burden (hours) could be made.
- In patients who were asymptomatic from their AF, an estimated AF burden was made using the twice daily ECG tracings that were transmitted.

Compliance with Alivecor cardiac monitor was measured by percentage of tracings transmitted over the expected number of tracings.

Diagnosis of AF-hospitalisations was made using initially using patient description of AF hospitalisation, during telephone or clinic follow up at the end of six months then confirmed by investigator on an electronic record that contains clinical information regarding patient hospitalisation.

Chapter 4

Electrophysiological analysis of the left atrium using renewal theory

4.1 Abstract

Background: Variations in LA regional structural and electrical remodelling have been observed between paroxysmal and persistent AF patients. It has been postulated that some of these regions may play a crucial role in AF persistence, for instance, the LA posterior wall. However, additional ablation procedures targeting these regions, particularly in persistent AF patients, have not yielded any additional clinical benefit. Using the renewal approach, we seek to understand the spatial distribution of renewal rate constants in the LA between different AF Phenogroups.

Methods: RENEWAL-AF is a prospective multicentre observational study recruiting AF ablation patients (ACTRN 12619001172190). Unipolar electrograms were obtained from ten LA locations using a 16-electrode Advisor TM HD-Grid catheter. Renewal rate constants λ_f, λ_d, and the rho (ρ) values (λ_f / λ_d) were calculated.

Results: Two groups were analysed; Phenogroup 1 (Ph1), highest ρ in pulmonary veins, Phenogroup 2 (Ph2), highest ρ in LA body. In all patients, and between different AF Phenogroups, correlations (r^2) between λ_f and λ_d were above 0.9 except in the LA low posterior wall in AF Phenogroup 2 (r^2=0.75). In all patients, the highest mean ρ was in the LA posterior wall and lowest in the pulmonary veins (1.26 ± 0.28 versus 1.19 ± 0.11, respectively). When both AF Phenogroups were compared, mean ρ value in the pulmonary veins were higher in AF Phenogroup 1 compared to AF Phenogroup 2 (1.25 ± 0.09 vs 1.16 ± 0.11, P=0.0008). In AF Phenogroup 1, highest mean ρ values were observed in the inferior pulmonary

veins (RIPV, 1.31 ± 0.14; LIPV, 1.30 ± 0.16) while in AF Phenogroup 2, the highest mean ρ values were observed in the LA low posterior wall (1.32 ± 0.65).

Conclusion: Renewal-based analysis of electrophysiologic properties of the LA revealed distinct spatial variations in renewal rate constants between AF Phenogroups. Defining statistically significant regions may be clinically useful to help dictate further ablation strategies beyond PVI.

4.2 Introduction

Atrial fibrillation is characterised by transient, unstable rotational circuits or rotors with complex, heterogenous wavefront activation patterns (75, 431, 463, 481). Despite the chaotic and turbulent nature of AF, earlier studies utilizing statistical methods analysing rotational circuits and wavefront activations have revealed a degree of organisation within AF (456, 560, 591). Further, spectral analysis of fibrillatory waves in animal and human AF models has also revealed specific atrial locations with high dominant frequencies, supporting the notion of an underlying organisation. For instance, in cholinergic AF in isolated sheep hearts, spectral wave analysis revealed high-frequency sources in the posterior wall of the LA (592). In paroxysmal AF patients, high dominant frequency sites are localised to the posterior LA and around the region of the ostia of the pulmonary veins (PV) (191). However, in persistent AF patients, higher dominant frequency sites have been observed distributed in other atrial regions, rather than the posterior wall of LA or the PV ostia (191).

Although various studies have shown regional differences in LA structural remodelling in patients with paroxysmal versus persistent AF, findings so far have failed to yield any consensus agreement as to which specific LA regions may be responsible for AF persistence. Using biatrial electroanatomic mapping, Chang et al showed in n=118 AF patients, a significantly lower LA voltage in the lateral LA wall, anterior and posterior LA roof in persistent AF, when compared to paroxysmal AF (593). Another smaller prospective study involving n=36 AF patients undergoing catheter ablation showed significantly lower bipolar voltages

during electroanatomic mapping not only on the LA posterior wall and LA roof, but also in the antrum of the RSPV, antrum of the RIPV and the LA septum (594). Using cardiac MRI in a retrospective study involving n=195 AF patients, Lee et al showed a significant association between the presence of LGE on the left inferior pulmonary vein and AF persistence (595).

In this study, we aim to define the spatial distribution of renewal rate constants throughout the left atrium, specifically between the different AF Phenogroups. Clinically, delineating the spatial distribution of the renewal rate constants, particularly in patients with AF Phenogroup 2 could potentially be crucial to identify atrial regions that could be attractive targets for ablation.

4.3 Methods

Patient population

N=41 patients with paroxysmal and persistent AF undergoing catheter ablation were studied. Ethics approval was by the Southern Adelaide Local Health Network Ethics Committee (HREC/19/SAC/292). All patients provided informed consent.

Electrophysiologic study

Electrophysiologic studies were conducted at least five half-lives free of antiarrhythmic drug therapy, whenever feasible, except in patients taking amiodarone. Patients were mapped under spontaneous or induced AF using the Ensite Precision electroanatomic mapping system (Abbott Cardiovascular, Plymouth MN). Electrograms and ECG were recorded at 1000 Hz, and unipolar electrogram filter band pass was set at 0.5-500 Hz. Sequential one-minute recordings of unipolar and bipolar electrograms were obtained using the Advisor^{TM} HD-Grid catheter (16 electrodes in a square grid catheter 13x13mm^2 grid, 3mm interelectrode-spacing, Abbott Cardiovascular, Plymouth MN) from sixteen different intracardiac locations; six RA locations, 1) Superior vena cava (SVC) – RA junction 2) RA appendage 3) RA septal region

4) RA posterior region 5) RA lateral region 6) RA cavotricuspid isthmus region and ten LA locations, 1) Left superior pulmonary vein 2) Left inferior pulmonary vein 3) Right superior pulmonary vein 4) Right inferior pulmonary vein 5) Left high posterior wall 6) Left low posterior wall 7) Left lateral region 8) LA appendage 9) LA anterior region and 10) LA septal region. Stability and contact between the catheter and LA endocardium were maintained throughout recordings through visualisation of the deformation of the HD-Grid catheter on the electroanatomic map on the LA endocardial border and the presence of sharp local electrograms on the tracings (Figure 3). A PVI-only radiofrequency ablation approach was performed by all operators. The endpoint of entrance and exit block from the pulmonary veins was confirmed post-ablation.

Signal processing

Unipolar electrogram signals were exported and processed as described previously (447, 457, 472). Sinusoidal recomposition was applied with the dominant frequency set as the wavelet period and phase computed using the Hilbert transform to construct phase maps (82, 447, 457, 472). In each phase map, phase singularities (PS) were detected and tracked as previously described using a convolution kernel method based on topological charge (447, 457, 472). PS tracking enabled the calculation of PS lifetimes and inter-formation times (times between consecutive PS formations), which also enabled the construction of PS lifetime and inter-formation time distributions (447, 457, 472). PS distributions were fitted using maximum likelihood fitting to estimate the rate of PS formation (denoted as λ_f) and PS destruction (denoted as λ_d) (447, 457, 472).

Statistical analysis

We first compared the association between λ_f and λ_d in all ten sampled LA regions. Associations between different anatomical regions were evaluated using Pearson's correlation coefficient. We proceeded to compare regional renewal rate constants between different AF Phenogroup. LA regions involved included

1) mean PV ρ 2) mean non-PV (LA body locations excluding LAA and PV) ρ 3) mean posterior wall (both high and low LA posterior wall) and the mean LAA. This was followed by individual LA locations. Differences between groups were examined using the χ^2 test and two group comparisons were analysed using student t-test. An example of a sampled atrial region is as presented in Figure 4.1. Data were reported as the mean ± SD (standard deviation, SD) and associated 95% confidence interval. Statistical analysis was performed using STATA 15.1 with α at $P < .05$.

4.4 Results

Association between rates of rotor formation and destruction in LA.

In all patients, the rates of λ_f and λ_d were highly correlated, with a degree of correlation, r^2 of above 0.9 (Table 4.1). When divided into AF Phenogroups, a similar degree of correlations and significance were observed (Table 4.2)

Spatial distribution of renewal rate constants

Analysis by LA regions

We then analysed the spatial distribution of renewal rate constants, ρ between different LA regions. When different LA regions were compared, the highest ρ was observed in the LAA region with a mean of 1.32 ± 0.26, 95% CI (1.22, 1.48) and the lowest ρ was observed in the posterior wall with a mean of 1.21 ± 0.12, 95% CI (1.17, 1.25) (Table 4.2). When both AF Phenogroups were compared, the mean ρ in both the pulmonary veins and the posterior wall were significantly higher in AF Phenogroup 1, when compared to AF Phenogroup 2 [1.37 ± 0.26, 95% CI (1.23, 1.51) versus 1.17 ± 0.11, 95% CI (1.12, 1.21), P=0.0015 and 1.26 ± 0.03, 95% CI (1.19, 1.33) versus 1.18 ± 0.1, 95% CI (1.14, 1.22), P=0.04, respectively)

Analysis by individual LA locations

In all patients: When analysed in each LA location, ρ was the highest in the LAA, 1.32 ± 0.26, 95% CI (1.22, 1.48) followed by RIPV with a mean ρ of 1.29 ± 0.4, 95% CI (1.16, 1.43). The lowest ρ was observed in the LA low posterior wall with a mean ρ of 1.20 ± 0.2, 95% CI (1.13, 1.26) (Table 4.3).

By AF Phenogroups: ρ value in AF Phenogroup 1 was the highest in the LIPV with a mean ρ of 1.35 ± 0.29, 95% CI (1.18, 1.51) followed by the LSPV with a mean ρ of 1.33 ± 0.26, 95% CI (1.19, 1.48), and the lowest in the LA anterior wall with a mean ρ of 1.21 ± 0.1, 95% CI (1.15, 1.26) (Table 4.3). In AF Phenogroup 2, we observed the highest ρ value in the LAA with a mean of 1.36 ± 0.3, 95% CI (1.22, 1.49) while the lowest ρ value was observed in the LIPV with a mean ρ of 1.12 ± 0.17, 95% CI (1.04, 1.18). When AF Phenogroups were considered, significantly higher ρ was observed in the region of the pulmonary veins in AF Phenogroup 1, compared to AF Phenogroup. Specifically, the mean ρ of RIPV, LIPV, RSPV and LSPV in AF Phenogroup 1 were significantly higher compared to AF Phenogroup 2 (1.31 ± 0.14 vs 1.14 ± 0.12, P=0.0009, 1.35 ± 0.29 vs 1.12 ± 0.17, P=0.003, 1.30 ± 0.28 versus 1.15 ± 0.15, P=0.04 and 1.33 ± 0.26 versus 1.19 ± 0.11, P=0.03) (Table 4.3).

4.5 Discussion

The main findings of this study include: -

1. ***In all AF patients, we observed the repetitive formation and annihilation of rotors which are highly correlated. Similar observations were made in patients from both AF Phenogroup 1(PV subtype) and AF Phenogroup 2 (LA body subtype).***

   We observed a high degree of correlation between the rates of formation and destruction of PS, in all LA regions. In addition, plotting a distribution of PS inter-formation and lifetime plot over time sampled always produced 1) exponential distributions characteristic of renewal processes (Figure 4.1) and 2) a “longer” lasting PS is always present in any LA region sampled (Figure 4.1), but every region consists of predominantly transient, and unstable short-lasting PS, consistent

with findings from previous studies (75, 596). Mechanistically, the high statistical correlation between the formation and destruction of PS in all LA regions (Table 4.1) suggests that AF is maintained by a continuous formation and destruction of PS (597), which can be quantified using the renewal approach. Findings from this study were consistent with observations made from earlier studies by Dharmaprani et al who statistically analysed rates of formation and destruction of rotors in computational, animal, and human models of AF and patients undergoing cardiac surgery with VF (16, 472).

2. ***In all AF patients, we observed the highest ρ value in the LAA, specifically in patients in AF Phenogroup 2, the non-PVI responsive subgroup.***

   There has been increasing clinical interest in LAA electrical isolation in AF patients. In 2010, a prospective study involving n=987 AF patients undergoing re-do catheter ablation for AF showed that approximately 27% of patients were found to have focal firing from the LAA. Patients who had circumferential ablation for LAA isolation appeared to have a lower rate of AF recurrences, compared to patients without additional LAA isolation (15% versus 74%, $P<0.001$), after 12 months of follow-up (598). Subsequently, a meta-analysis that looked at the clinical benefit of LAA electrical isolation in n=7 studies involving 930 non-paroxysmal AF patients also showed significantly improved overall freedom from atrial arrhythmia recurrence at 12 months in patients who underwent LAA electrical isolation, versus patients who had standard ablation performed (75.5% versus 43.9%, $P<0.0001$) (155). Embryologically, it has been previously suggested that the LAA behaves similarly to the pulmonary veins in initiating episodes of AF (599). An earlier study has observed changes in the LAA emptying and filling velocities, in the setting of acute changes in loading conditions in canine models subjected to volume expansion (600). Mechanistically, it has been suggested that significant structural remodelling in the LAA occurs in the setting of elevated

LA pressure, which may contribute to electrophysiological changes that would favour AF maintenance (601).

In addition, the role of epicardial connections between the pulmonary veins and the LAA has been suggested as a potential cause. For instance, the ligament of Marshall is an epicardial connection between the coronary sinus and the LAA and the left superior pulmonary veins, which contain both sympathetic and parasympathetic nerves that may trigger episodes of AF (148). On the other hand, Bachmann's bundle which has several muscular connections to the base of the LAA may also be responsible for the rapid activation of AF from the LA to the RA (480). Some studies have also shown associations between echocardiographic evidence of loss of function in the LAA and increased size of LAA volume and orifice area, with atrial tachyarrhythmia recurrences after catheter ablation in AF patients (602, 603). A prospective study involving n=83 AF patients undergoing de-no AF ablation procedure, the presence of LAA mechanical dysfunction, measured using LAA ejection fraction of less than 44.68%, was a stronger predictor for AF recurrence, when compared to LAA volume above 9.25 ml (sensitivity of 90% and specificity of 67.4% versus sensitivity of 85.2% and specificity of 67.9%, respectively) (604)Conversely, preserved LAA ejection fraction protective against AF recurrence post catheter ablation (602) Mechanistically, it has been suggested that significant structural remodelling in the LAA occurs in the setting of elevated LA pressure, which may contribute to electrophysiological changes that would favour AF maintenance (601).

3. ***We observed a significantly higher ρ value in the posterior wall in AF Phenogroup 1 patients, compared to AF Phenogroup 2***

These findings correlate with our current anatomical and mechanistic understanding of the role of the posterior wall in AF. Electrically, cardiomyocytes in the LA posterior wall possess unique electrophysiological properties, which increase their susceptibility to electrical misfiring.

Specifically, these cardiac cells have a short action potential duration, low resting membrane potential and the shortest refractory period, when compared to cardiomyocytes from other cardiac regions (136). Two autopsy studies have observed the presence of a posterior wall thickness gradient, with the thinnest portion being the superior posterior wall and the thickest portion around the inferior posterior wall between the pulmonary veins (605, 606). This is an important finding as increased atrial wall thickness has previously been associated with AF persistence (607). This observation of a higher ρ value in the posterior wall region could also be explained by multiple confounding extra-cardiac features. The ganglionic plexi (an epicardial neural network that provides cardiac sympathetic and parasympathetic innervation) which has been implicated in AF persistence, are located in the vicinity of the LA posterior wall (137). A higher amount of epicardial fat surrounding the region of the LA posterior wall has also been shown to be an independent predictor of AF (138) and has been associated with low voltage zones around this region, which could contribute to AF initiation and persistence (139). Furthermore, another study has suggested the presence of atrial remodelling around the region of the LA low posterior wall is a consequence of its proximity to the thoracic descending aorta. In a study of n=109 AF patients undergoing AF ablation, who underwent quantification of LA fibrosis using pre-procedural CMR-LGE, a significantly higher degree of atrial fibrosis in the posterior wall, the extent of which correlated with greater aortic distensibility and a closer distance between LA and descending aorta (608).

4. ***In AF Phenogroup 1 AF patients, we observed a higher ρ value in all four pulmonary veins, when compared to AF Phenogroup 2 patients.***

Pulmonary vein musculature possesses intrinsic structural and electrical properties that predispose to arrhythmogenesis. Earlier studies have shown that cardiomyocytes in the pulmonary vein have shorter refractory periods compared to other atrial regions. This is

secondary to a higher density of I_{Ks}- and I_{Kr}- ion cells and a lower density of I_{Ca2} ion cells in this region (165). Additionally, regulation of these ionic channels is also dependent on autonomic nervous system innervation (both sympathetic and parasympathetic stimulation results in a shorter effective refractory period (609), which is found in abundance around the pulmonary muscular sleeves (497). Structurally, a heterogeneous myofiber arrangement and direction in the pulmonary veins promoting re-entry and the presence of pulmonary vein hypertrophy and fibrosis have been hypothesised as the major mechanisms of arrhythmogenesis (574, 610).

4.6 Conclusion

Renewal theory-based analysis of electrophysiological properties in the left atrium revealed distinct variations in the spatial distribution of renewal rate constants in the LA, between AF Phenogroup 1 and AF Phenogroup 2. The regional variations observed are likely a result of spatial anatomical and electrophysiological heterogeneity that occurs secondary to atrial remodelling, which plays a crucial role in AF initiation and maintenance.

4.7 Tables

Table 4.1: Degree and significance of correlations between λ_f and λ_d in all ten LA regions sampled, in all patients and between different AF Phenogroups.

LA locations	**Correlation between λ_f and λ_d in all patients (n=41)**	**Correlation between λ_f and λ_d (AF Phenogroup 1) (n=16)**	**Correlation between λ_f and λ_d (AF Phenogroup 2) (n=25)**
LAA	r^2=0.94, P<0.001	r^2=0.96, P<0.001	r^2=0.93, P<0.001
LA septal	r^2=0.98, P<0.001	r^2=0.97, P<0.001	r^2=0.98, P<0.001
LA anterior	r^2=0.95, P<0.001	r^2=0.97, P<0.001	r^2=0.98, P<0.001
LA high posterior wall	r^2=0.99, P<0.001	r^2=0.98, P<0.001	r^2=0.99, P<0.001
LA low posterior wall	r^2=0.98, P<0.001	r^2=0.91, P<0.001	r^2=0.99, P<0.001
LA lateral	r^2=0.99, P<0.001	r^2=0.99, P<0.001	r^2=0.97, P<0.001
LIPV	r^2=0.98, P<0.001	r^2=0.99, P<0.001	r^2=0.99, P<0.001
LSPV	r^2=0.98, P<0.001	r^2=0.98, P<0.001	r^2=0.99, P<0.001
RIPV	r^2=0.99, P<0.001	r^2=0.99, P<0.001	r^2=0.99, P<0.001
RSPV	r^2=0.91, P<0.001	r^2=0.96, P<0.001	r^2=0.98, P<0.001

Data presented by degree of significance, r^2 and their associated P-values in all LA regions sampled, according to AF Phenogroups.

Table 4.2: Comparison between mean ρ in all patients, and between AF Phenogroups comparing different LA regions

LA location	All patients (n=41)	AF Phenogroup 1 (n=15)	AF Phenogroup 2 (n=25)	P-value
Mean PV ρ	1.25 ± 0.2 95% CI (1.18, 1.31)	1.37 ± 0.26 95% CI (1.23, 1.51)	1.17 ± 0.11 95% CI (1.12, 1.21)	0.0015
Mean non-PV ρ	1.24 ± 0.08 95% CI (1.21, 1.26)	1.26 ± 0.09 95% CI (1.21, 1.30)	1.22 ± 0.08 95% CI (1.19, 1.25)	0.15
Mean posterior wall ρ	1.21 ± 0.12 95% CI (1.17, 1.25)	1.26 ± 0.03 95% CI (1.19, 1.33)	1.18 ± 0.1 95% CI (1.14, 1.22)	0.04
Mean LAA ρ	1.32 ± 0.26 95% CI (1.24, 1.40)	1.27 ± 0.16 95% CI (1.18, 1.35)	1.36 ± 0.3 95% CI (1.22, 1.49)	0.29

Data presented as mean ± standard deviation and their associated 95% confidence interval. Non-PV includes all sampled non-pulmonary vein locations.

Table 4.3: Comparison between mean ρ in all sampled left atrial locations, between AF Phenogroup 1 and AF Phenogroup 2.

LA locations	All patients (n=41)	AF Phenogroup 1 (n=16)	AF Phenogroup 2 (n=25)	P-value
LAA	1.32 ± 0.26 95% CI (1.22, 1.48)	1.27 ± 0.16 95% CI (1.18, 1.35)	1.36 ± 0.3 95% CI (1.22, 1.49)	0.29
LA septum	1.21 ± 0.11 95% CI (1.17, 1.24)	1.25 ± 0.12 95% CI (1.18, 1.31)	1.18 ± 0.1 95% CI (1.14, 1.22)	0.07
LA anterior	1.22 ± 0.11 95% CI (1.18, 1.25)	1.21 ± 0.1 95% CI (1.15, 1.26)	1.22 ± 0.12 95% CI (1.17, 1.28)	0.65
LA high posterior	1.22 ± 0.19 95% CI (1.16, 1.28)	1.27 ± 0.2 95% CI (1.16, 1.38)	1.19 ± 0.19 95% CI (1.11, 1.27)	0.2
LA low posterior	1.20 ± 0.2 95% CI (1.13, 1.26)	1.22 ± 0.22 95% CI (1.10, 1.33)	1.19 ± 0.2 95% CI (1.10, 1.27)	0.64
LA lateral	1.23 ± 0.12 95% CI (1.19, 1.27)	1.26 ± 0.11 95% CI (1.19, 1.32)	1.22 ± 0.12 95% CI (1.16, 1.27)	0.33
LSPV	1.25 ± 0.2	1.33 ± 0.26	1.19 ± 0.11	0.03

	95% CI (1.18, 1.31)	95% CI (1.19, 1.48)	95% CI (1.14, 1.24)	
LIPV	1.2 ± 0.25 95% CI (1.12, 1.28)	1.35 ± 0.29 95% CI (1.18, 1.51)	1.12 ± 0.17 95% CI (1.04, 1.18)	0.003
RSPV	1.21 ± 0.23 95% CI (1.14, 1.29)	1.30 ± 0.28 95% CI (1.15, 1.46)	1.15 ± 0.15 95% CI (1.08, 1.22)	0.04
RIPV	1.29 ± 0.4 95% CI (1.16, 1.43)	1.31 ± 0.14 95% CI (1.14, 1.75)	1.14 ± 0.12 95% CI (1.14, 1.22)	0.0009

Data presented as mean ± standard deviation, 95% confidence interval and their associated P-values.

4.8 Figures

Figure 4.1: Correlation between λ_f and λ_d in the LAA

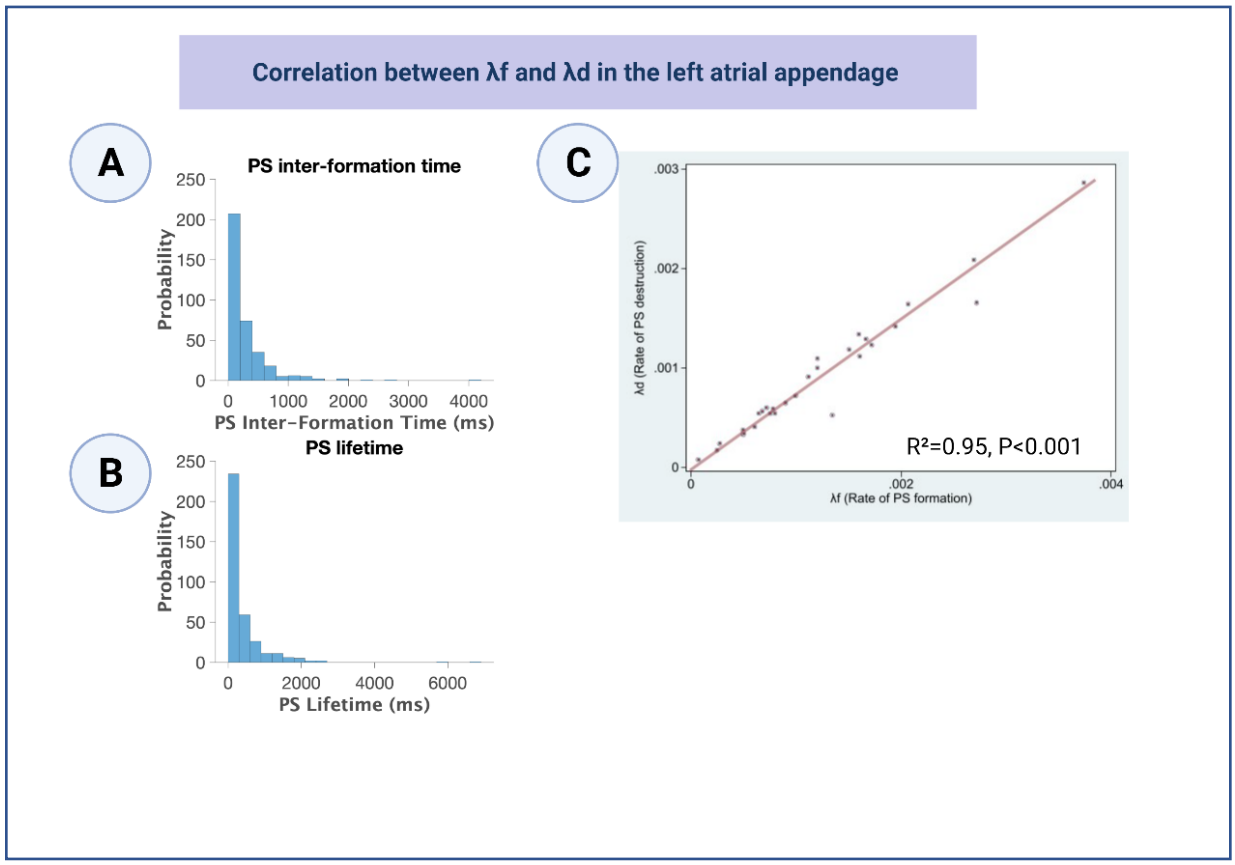


Figure 4.1 showing in A) and B) an exponential population distribution of formation (inter-formation) and destruction (lifetimes) of phase singularities in the LAA and in C) a high correlation between the rates of formation and destruction of phase singularities in the LAA, suggesting phase singularities n AF are continuously formed and destroyed (r^2=0.94, P<0.001).

Chapter 5

Relationship between renewal-based electrophysiological analysis of the left atrium and echocardiographic markers of structural and functional remodelling

5.1 Abstract

Background: The associations of LA structural and functional remodelling with AF persistence have been well described. In AF, LA structural and functional remodelling have been linked to adverse cardiovascular outcomes, failure of anti-arrhythmic therapy and recurrences of AF post cardioversion and ablation. We have recently observed an association of adverse clinical outcomes with AF Phenogroup, a novel approach to electrophysiologic characterisation of AF based on the renewal theory. In this study, we seek to explore the association between AF Phenogroup and echocardiographic features of LA structural and functional remodelling.

Methods: RENEWAL-AF is a prospective multicentre observational study recruiting AF ablation patients (ACTRN 12619001172190). Unipolar electrograms were obtained from ten LA locations using a 16-electrode Advisor TM HD-Grid catheter. Renewal rate constants λ_f, λ_d, and the rho (ρ) values (λ_f / λ_d) were calculated. Echocardiographic assessment and LA phasic analysis were performed pre-ablation in all patients.

Results: Mean indexed LA volume was 42.9 ± 8.5 ml^3/m^2 and the mean LA ejection fraction (EF) was 39.2 ± 13.0 % in AF Phenogroup 2 had a higher indexed LA volume and a lower minimum 3D compared to AF Phenogroup 1 (45.1 ± 8.9 versus 39.3 ± 6.4, P=0.039 and 33.6 ± 10.2 versus 48.3 ± 22.3, P=0.05). The

presence of LA mechanical dysfunction, defined as LA ejection fraction of less than 45%, trended towards significance in AF Phenogroup 2 patients (P=0.06). In addition, diastolic dysfunction was also more prevalent in AF Phenogroup 2 than AF Phenogroup 1 patients (12 (48%) versus 2(13%), P=0.035).

Conclusion: Findings from RENEWAL-AF suggest a link between AF Phenogroup 2 (LA body subtype) with adverse markers of structural and functional remodelling in the left atrium.

5.2 Introduction

Progressive atrial structural and functional adverse remodelling underlies our current understanding of AF progression and persistence (108, 611). LA enlargement, a marker of LA structural remodelling, has been shown to be associated with adverse cardiovascular outcomes in AF patients, including stroke and increased mortality, antiarrhythmic treatment failure, as well as early AF recurrence post cardioversion and catheter ablation (612-617). In addition, there has also been an increasing recognition of the importance of functional LA remodelling.(618) Echocardiographic markers of LA functional remodelling have increasingly been used to predict incident AF and have also been associated with negative clinical outcomes post catheter ablation (619-621). Physiologically, both LA structural and functional remodelling are closely related, where loss of LA function occurs with progressive LA dilatation, and atrial fibrotic deposition because of arrhythmia persistence or underlying medical comorbidities (611, 622).

A common observation in AF is the continuous formation and destruction of rotors, which follows an exponential distribution (82, 461, 463, 465). This exponential distribution is characteristic of a phenomenon displaying a renewal process, a branch of probabilistic theory in mathematics (520, 623). Importantly, the renewal theory suggests that despite the statistically independent formation and destruction processes of rotors, these events eventually converge to a predictable probability distribution (520, 623). We have recently shown in animal, computational and human AF and VF models, renewal theory can be applied to accurately predict the probability distributions of rotor formation and lifetimes

(16, 457, 472). In earlier chapters, we observed that characterising a patient's AF Phenogroup could potentially be clinically used to predict responsiveness to PVI-only procedure. In this chapter, we seek to explore the association between echocardiographic markers of adverse LA structural and functional remodelling, with AF Phenogroup, a novel AF electrophysiologic characterisation based on the renewal theory.

5.3 Methods

Patient population

N=41 patients with paroxysmal and persistent AF undergoing catheter ablation were studied. Ethics approval was by the Southern Adelaide Local Health Network Ethics Committee (HREC/19/SAC/292). All patients provided informed consent.

Echocardiographic study

Transthoracic echocardiogram (TTE) was performed in all patients prior to their AF ablation procedure using a Vivid E95 ultrasound system. All measurements were made according to the American Society of Cardiology Guidelines. LV function volumes and function were calculated using the modified Simpsons method. LA volume was measured using modified Simpson's method using apical two and four chamber views at the end of systole preceding the opening of mitral valve and then indexed to body surface area (BSA) to obtain left atrial volume index (LAVi). 3D LA volumes were measured, depending on clarity of LA endocardial borders. Early (E) and late (A) trans mitral velocities were calculated using the apical four chamber view by placing the sample volume at the tip of mitral valve leaflets, while the peak septal and lateral mitral annular velocities (e') were obtained using tissue doppler imaging (TDI). Left ventricular filling pressures were assessed by dividing the E wave by the average e' velocities (E/e'). Diastolic assessment was assessed as according to the JASE guidelines 2016 (269). In the LA, speckle tracking was performed from the apical four chamber, apical two chamber and parasternal long axis views using Q-

analysis (EchoPac Version 202, GE Vingmet Ultrasound) (269). Tracking was performed along the entirety of the LA endocardial border, adjusted to cover the entire LA throughout the cardiac cycle. Studies were deemed inadequate for analysis and excluded when any part of the tracking is unable to follow the LA endocardial border completely. LA reservoir, conduit, contractile function along with LA ejection fraction were determined using the EACVI/ASE/Industry Task Force recommendations to standardize deformation imaging (269), using QRS wave onset as the starting point for LA strain analysis (Figure 5.1),

1. LA conduit phase: First positive peak occurring at mitral valve opening. In sinus rhythm, the conduit phase continues through diastasis until the beginning of LA contraction while in AF, the conduit phase continues until the onset of mitral valve closure or the offset of ventricular diastole.
2. LA contractile phase: First negative peak occurring at maximal LA contraction. It begins at the onset of LA contraction and ends at the onset of mitral valve closure or at the end of ventricular diastole. This is only measured in patients in sinus rhythm.
3. LA reservoir phase: Begins at the end of mitral valve closure (at the end of ventricular diastole) and ends at the onset of mitral valve opening. Physiologically, it represents the duration of LV isovolumic contraction, ejection, and relaxation. The difference between the positive and negative strain peaks represents LA reservoir function.
4. LA ejection fraction was calculated using the formula (LA V max – LA V min / LA V max x 100%).

Electrophysiologic study

Electrophysiologic studies were conducted at least five half-lives free of anti-arrhythmic drug therapy, whenever feasible, except in patients taking amiodarone. Patients were mapped under spontaneous or induced AF using the Ensite Precision electroanatomic mapping system (Abbott Cardiovascular, Plymouth MN). Electrograms and ECG were recorded at 1000 Hz, and unipolar electrogram filter band pass was set at 0.5-500 Hz. Sequential one-minute recordings of unipolar and bipolar electrograms were obtained using the Advisor^{TM} HD-Grid catheter (16 electrodes in a square grid catheter 13x13mm^2 grid, 3mm interelectrode-spacing, Abbott Cardiovascular, Plymouth MN) from ten different intracardiac locations; ten LA locations, 1) Left superior pulmonary vein 2) Left inferior pulmonary vein 3) Right superior pulmonary vein 4) Right inferior pulmonary vein 5) Left high posterior wall 6) Left low posterior wall 7) Left lateral region 8) LA appendage 9) LA anterior region and 10) LA septal region. Stability and contact between catheter and LA endocardium were maintained throughout recordings through visualisation of deformation of the HD-Grid catheter on the electroanatomic map on LA endocardial border and presence of sharp local electrograms on the tracings.

Signal processing

Unipolar electrogram signals were exported and processed as described previously (447, 457, 472). Sinusoidal recomposition was applied with the dominant frequency set as the wavelet period and phase computed using the Hilbert transform to construct phase maps (82, 447, 457, 472). In each phase map, phase singularities (PS) were detected and tracked as previously described using a convolution kernel method based on topological charge (447, 457, 472). PS tracking enabled calculation of PS lifetimes and inter-formation times (times between consecutive PS formations), which also enabled construction of PS lifetime and inter-formation time distributions (447, 457, 472). PS distributions were fitted using

maximum likelihood fitting to estimate the rate of PS formation (denoted as λ_f) and PS destruction (λ_d) (447, 457, 472).

Statistical analysis

Data was reported as the mean (standard deviation, SD). Categorical variables were presented as n (%) and differences between group were examined using the χ^2 test. Two group comparisons were analysed using student t-test. Statistical analysis was performed using STATA 15.1 with α at $P < .05$.

5.4 Results

LA structural characteristics

In all patients, the mean indexed LA volume (ml^3/m^2) was 42.9 ± 8.5, 95% CI 40.1 45.7, minimum 3D LA volume (ml^3) was 43.4 ± 20.3, 95% CI 36.2 50.6 and the maximum 3D LA volume (ml^3) was 68.6 ± 20.4, 95% CI 60.9 75.4 (Table 5.1). When both AF Phenogroups were compared, the mean indexed LA volume (ml^3/m^2) and the mean minimum 3D LA volume was significantly higher in AF Phenogroup 2 compared to AF Phenogroup 1 (45.1 ± 8.9 versus 39.3 ± 6.4, P=0.039; 48.3 ± 22.3 versus 33.6 ± 10.2, P=0.05, respectively) (Table 5.2).

LA functional characteristics

In all patients, the mean LA ejection fraction (%) was 39.2 ± 13.0, 95% CI 35 43.4, mean LA conduit (%) was -11.1 ± 4.9, 95% CI -12.7 -9.5, mean LA reservoir (%) was 18.4 ± 9.6, 95% CI 15.3 21.5, and the mean LA contractile (%) was -6.0 ± 12.7, 95% CI -10.6 -2.4 (Table 5.3). When both AF Phenogroups were compared, no significant differences were observed between LA ejection fraction (%), LA conduit (%), LA reservoir (%) and LA contractile (%) in between both phenogroups (41.2 ± 14.5 versus 37.8 ± 12.0, P=0.43, -11.1 ± 5.4 versus -11.1 ± 4.9, P=0.99; 18.5 ± 13 versus 18.4 ± 7.1, P=0.96; -5.4 ± 19.4 versus -6.8 ± 6.0, P=0.68) (Table 5.4).

LA diastolic function characteristics

In all patients, the measured mean mitral E velocity (cm/s) was 66.2 ± 4.3, 95% CI 57.4 74.9, mean E/e', as a surrogate of LV filling pressures, was 8.5 ± 3.3, 95% CI 7.5 9.6, and the mean E/A ratio was 1.6 ± 1.5, 95% CI 1.0 2.1. Diastolic dysfunction, measured using the JASE 2016 criteria, was present in 14 (34%) of patients (Table 5.5). When both AF Phenogroups were compared, there was a significantly higher prevalence of diastolic dysfunction in AF Phenogroup 2 compared to Phenogroup 1 (12(48%) versus

2(13%), P=0.035) with no significant differences observed in the LV filling pressures, measured by E/e' and mean E/A ratio (7.9 ± 2.3 versus 8.9 ± 3.6, P=0.39; 1.3 ± 0.3 versus 1.7 ± 1.8, P=0.42) respectively (Table 5.6).

Association between LA structural and functional remodelling with AF Phenogroup

We further analysed the association between AF Phenogroups and LA structural and functional remodelling, as binary variables.

We defined LA dysfunction is defined as LA ejection fraction less than 45%, LA enlargement was defined as indexed LA volume > 40 ml^3/m^2, LV subclinical systolic dysfunction is defined as LV GLS > -17 and LA dysfunction and enlargement include AF patients with both evidence of enlarged LA (indexed LA volume > 40 ml^3/m^2) and LA dysfunction (LA ejection fraction less than 45%) (Table 5.7).

We observed a higher proportion of patients in AF Phenogroup 2, compared to Phenogroup 1 with evidence of LA structural remodelling, measured by indexed LA volume > 40 ml^3/m^2 in n=13 (54.2%) versus n=1 (9.1%), P=0.015, respectively but LA functional remodelling, measured by LA ejection fraction, was non-significantly higher in patients in AF Phenogroup 2 with n=16(66.7%) versus n=5(35.7%), P=0.06, respectively. A combination of LA structural and functional remodelling was also significantly higher in patients in AF Phenogroup 2 compared to AF Phenogroup 1, with n=13(54.2%) versus n=1(9.1%), respectively with P=0.012.

5.5 Discussion

The main findings from this study include: -

1) ***In AF Phenogroup 2 patients, we observed a significantly larger LA size, measured by indexed LA volume, a marker of LA structural remodelling.***

LA enlargement is an established structural marker of LA remodelling. In animal studies, the prevalence of AF is higher in larger than smaller animals. In rodent models of AF, it has been previously shown that AF can only be induced in rodents with atrial chamber areas greater than 1000 mm^2 (624, 625). In larger animals, AF is much easily inducible in models with pressure or volume overload, rapid atrial pacing, and myocardial ischemia (625). In addition, in porcine models of AF, a reduction in atrial effective refractory period (ERP) has been observed with increased atrial surface area (626). This has led to the notion that a critical mass of atrial tissue is required to sustain fibrillation in humans. Interestingly, such observations have also been made in multiple biological and physical systems demonstrating spatiotemporal chaos (627, 628). In chaotic systems, the number of "instabilities" increase with increasing domain size as this introduces different forms of wavefront excitations, with different wavefront directions, and propagations and boundary states, resulting in a more spatially complex structure (629). Not surprisingly, controlling system size in experimental models of chaotic systems has also been shown previously to be effective in modulating the degree of chaos (630).

The earliest AF study by Garrey et al observed that AF was more easily inducible in larger tissue masses, but below a threshold size, fibrillatory activity was unable to be sustained (584). A more recent computational modelling study of AF has shown the presence of significantly higher wave breaks and electrical re-entry in larger cardiac tissue masses (631). Similarly, larger LA volumes are observed in taller individuals, youth with larger body surface area and obese individuals have all been postulated to contribute to AF susceptibility (632, 633). The risk of AF is also higher in athletes who undergo endurance exercise, where LA volume and diameter were observed to be significant predictors for AF (634, 635). In addition, multiple other cardiac comorbidities which induces pressure and/or volume overload on the LA have shown to contribute towards AF, including hypertension, valvular heart disease and LV systolic and diastolic dysfunction.

Histologically, an increase in cardiomyocyte cell size, accumulation of both intracellular glycogen and protein have all been observed (90, 280, 636). Importantly, a study by Kojodjojo et al showed a disconnect between the severity of atrial electrical and structural remodelling in human AF (302). In n=59 paroxysmal and persistent AF patients undergoing LA ablation for Wolff-Parkinson White syndrome, atrial effective refractory period and conduction slowing in multiple atrial locations were equally impaired in both groups, but with evidence of significant LA dilatation in the persistent AF group (302). This suggest markers of atrial structural remodelling may be a more sensitive marker of adverse LA remodelling compared to markers of atrial electrical remodelling.

More recently, there has been an increase in the use of three-dimensional echocardiography (3DE), particularly using echocardiographic methods such as maximal and minimal LA volume, which overcomes the limitation of two-dimensional echocardiography's (2DE) foreshortening and geometric assumptions to better estimate LA size (637). Not surprisingly, 3DE LA volumetric assessment has been shown to correlate better with LA volumes measured on CMR, and cardiovascular outcomes (638, 639), when compared to 2-DE LA volumetric assessment using Simpson's biplane method, which underestimates LA volume (640).

Study findings: Indexed LA volume was significantly lower in AF Phenogroup 1 patients (P=0.04). In addition, we also observed lower minimal LA volume in AF Phenogroup 1 compared to AF Phenogroup 2 (P=0.05), with no significant differences observed in the maximal LA volume (P=0.2) between both groups. Physiologically, this discrepancy can be explained by the different phases of cardiac cycle that occurs during these LA measurements. Maximal LA volume is influenced by ventricular systole, where longitudinal contraction of the LV leads to a downward displacement of the mitral valve annulus, hence, invariably a larger LA size (641). However, minimal LA volume is measured at the end of ventricular diastole, just at the onset of mitral valve closure, where the LA size is influenced by higher left ventricular end diastolic pressure (642). Not surprisingly, minimum LA volume has been shown to be associated with

higher N-terminal pro-B-type natriuretic peptide levels (643), echocardiographic markers of elevated LV filling pressures such as a higher E/e' level (642), and adverse cardiovascular outcomes in HFpEF patients (644). From a mechanistic standpoint, higher LV filling pressures occur in medical conditions that are known to predispose to AF such as hypertension, which results in an increase in LA pressures, LA wall stretch and subsequently, LA structural and functional remodelling.

2) ***In AF Phenogroup 2 patients, there was evidence of LA functional remodelling, measured by LA ejection fraction, a marker of LA functional remodelling.***

Three distinct phases in atrial function have been described (645). In the first phase, during mitral valve closure, and LV contraction or ventricular systole, there is filling of the LA with pulmonary venous return. In the second phase, LA acts as a conduit, when mitral valves open, with emptying of the LA into the LV, via passive suction of the LV cavity. The final phase, LA contraction occurs at the end of ventricular diastole, just before closure of the mitral valve, which contributes to approximately 15-30% of LV stroke volume. Another echocardiographic method to estimate LA function is through the calculation of LA ejection fraction, which is equivalent of the maximal LA volume – minimal LA volume / maximal LA volume x 100%.

Study findings: In our study, we observed a trend towards significance of a lower LA ejection fraction in AF Phenogroup 2 patients compared to AF Phenogroup 1 patients, when LA dysfunction was defined as LA ejection fraction less than 45% (P=0.06). However, no significant differences in other LA phasic function, including LA reservoir, conduit or contractile function between AF Phenogroup. The presence of LA mechanical dysfunction, defined as LA ejection fraction of less than 45% observed in AF Phenogroup 2 patients is likely attributed to the minimum LA volume in this cohort, which is non-significantly higher in AF Phenogroup 2 (47.9 ± 4.9 versus 34.3 ± 3.1, P=0.07) compared to the maximal LA volume measures

(71.8 ± 4.8 versus 62.1 ± 4.1, P=0.2). A previous prospective study involving n=574 participants, mean age of 74 years has shown that a lower LA ejection fraction was independently associated with a higher risk of AF or atrial flutter (267). This was driven mainly by a lower minimum LA volume, when compared to a maximum LA volume echocardiographic value (646). Importantly, a lower LA ejection fraction has also been associated with adverse cardiovascular outcomes. In n=146 persistent AF patients undergoing cardioversion, LA ejection fraction was an independent and significant predictor of sinus rhythm maintenance after 12 months follow up (647). In another prospective study involving n=140 heart failure with preserved ejection fraction (HFpEF) patients versus n=44 controls, a significantly lower LA ejection fraction was observed in HFpEF patients compared to controls (P<0.001) and was independently associated with heart failure hospitalisations or death after a median follow up of 1429 days (648). Finally, a more recently published retrospective study involving n=80 paroxysmal AF patients who underwent catheter ablation and pre-procedural CMR, showed a significantly lower LA ejection fraction in patients with recurrent AF post catheter ablation after a mean of four years follow up (649).

Interestingly, no significant differences were observed between phasic LA function between AF Phenogroup 1 and 2 patients. A lower LA reservoir strain, conduit strain and contractile strain measured using CMR have been observed in AF patients, when compared to patients in sinus rhythm and in patients with higher degrees of LA fibrosis (650). Furthermore, a lower LA strain has been shown to be predictive of new-onset AF both in a community level and in patients who were hospitalised with acute heart failure (268, 651). Compared to patients with paroxysmal AF, persistent AF patients have been shown to have a lower reservoir, conduit and contractile function, which corresponded to a significant atrial fibrosis, when measured using CMR feature tracking and LGE (652). The lack of difference observed between the two Phenogroups could be due to a few factors: 1) small number of patients included in the analysis 2) a variety of patient subgroups and demographics were included, given all patients who were eligible and referred for catheter ablation were included in the analysis.

3) <u>Diastolic dysfunction is more common in AF Phenogroup 2 compared to AF Phenogroup 1.</u>

In patients with diastolic dysfunction, the primary issue lies in impaired ventricular relaxation and reduced ventricular compliance. This results in 1) increase LA afterload, which is the pressure in the left ventricle that the LA must contract against 2) increased LA preload, which occurs when increased LV filling pressures results in pressures transmitted back into the LA during early LA filling phase and 3) LA, being a thin walled cardiac structure, responds to pressure and volume overload through LA dilatation (653). Community based studies have shown a link between the presence of diastolic dysfunction and new-onset AF. Tsang et al retrospectively examined n=840 participants over a mean of 4.1 years and observed a higher risk of developing AF in patients with evidence of abnormal LV relaxation, pseudo-normal and restrictive LV filling patterns with a HR of 3.33 (95% CI, 1.5-7.4, P=0.003), 4.84 (95% CI, 2.05-11.4, P<0.001) and 5.26 (95% CI, 2.3-12.03, P<0.001) respectively, when compared to patients with normal echocardiographic diastolic parameters (654). Interestingly, only LA volume index was a significant predictor of AF in this cohort, but not other individual echocardiographic measures of diastolic dysfunction (654). Another community based study involving n=4480 participants were prospectively followed for a mean of 12 years, and observed the association between echocardiographic markers of diastolic dysfunction, including increased trans-mitral E wave velocity, LA dimension and trans-mitral A wave velocity time integral with a higher risk of new onset AF (655).

Study findings: In our study, we observed a higher prevalence of diastolic dysfunction in patients in AF Phenogroup 2, compared with patients in AF Phenogroup 1 (n=12(48%) versus n=2(13%), P=0.035). When considering individual echocardiographic markers of diastolic dysfunction, LA volume index was significantly higher in AF Phenogroup 2 compared to AF Phenogroup 1 (45.1 ± 8.9 versus 38.8 ± 7.0, P=0.039), but no other individual echocardiographic markers of diastolic dysfunction met statistical

significance, consistent with findings by Tsang et al as discussed above (654). Clinically, the presence of diastolic dysfunction in AF patients has also been associated with negative clinical outcomes post catheter ablation procedures (656, 657)

5.6 Conclusion

AF Phenogroup electrophysiological classification based on renewal theory, specifically AF Phenogroup 2 was associated with diastolic dysfunction and known adverse echocardiographic markers of LA structural and functional remodelling.

5.7 Tables

Table 5.1: Echocardiographic markers of LA structural remodelling in all patients

LA structural measures	Mean ± SD	95% CI
Indexed LA volume (ml^3/m^2)	42.9 ± 8.5	40.1, 45.7
Minimum 3D LA volume (ml^3)	43.4 ± 20.2	36.2, 50.6
Maximum 3D LA volume (ml^3)	68.2 ± 20.4	60.9, 75.4

Table 5.1 showing LA structural echocardiographic measures in all patients. Data presented in mean ± standard deviation and their associated 95% confidence interval.

Table 5.2: Echocardiographic markers of LA structural remodelling comparing different AF Phenogroups.

LA structural measures	AF Phenogroup 1	95% Confidence Interval	AF Phenogroup 2	95% Confidence Interval	P-value
Indexed LA volume (ml^3/m^2)	39.3 ± 6.4	35.6, 43	45.1 ± 8.9	41.2, 48.8	0.039
Minimum 3D LA volume (ml^3)	33.6 ± 10.2	26.8, 40.5	48.3 ± 22.3	38.4, 58.1	0.05
Maximum 3D LA volume (ml^3)	60.1 ± 14.4	50.5, 69.8	72.2 ± 22.1	62.4, 82	0.11

Table 5.2 showing LA structural echocardiographic measures comparing different AF Phenogroups. Data presented in mean ± standard deviation.

Table 5.3: Echocardiographic markers of LA functional remodelling in all patients

LA functional measures	Mean ± SD	95% Confidence Interval
LA ejection fraction (%)	39.2 ± 13.0	35, 43.4
LA conduit (%)	-11.1 ± 4.9	-12.7, -9.5
LA reservoir (%)	18.4 ± 9.6	15.3, 21.5
LA contractile (%)	-6.5 ± 12.6	-10.6, -2.4

Table 5.3 showing LA functional echocardiographic measures in all patients. Data presented in mean ± standard deviation and their associated 95% confidence interval.

Table 5.4: Echocardiographic markers of LA functional remodelling comparing different AF Phenogroups.

LA functional measures	AF Phenogroup 1	95% Confidence Interval	AF Phenogroup 2	95% Confidence Interval	P-values
LA ejection fraction (%)	41.2 ± 14.5	33.2, 49.3	37.8 ± 12.0	32.8, 42.9	0.43
LA conduit (%)	-11.1 ± 5.4	-14, -8	-11.1 ± 4.9	-13.1, -9	0.99
LA reservoir (%)	18.5 ± 13	11.3, 25.7	18.4 ± 7.1	15.4, 21.4	0.96
LA contractile (%)	-5.4 ± 19.4	-16.2, 5.3	-6.8 ± 6.0	-9.6, -4.7	0.68

Table 5.4 showing LA functional echocardiographic measures comparing different AF Phenogroups. Data presented in mean ± standard deviation.

Table 5.5: Echocardiographic markers of diastolic dysfunction in all patients

LA functional measures	Mean ± SD or n (%)	95% Confidence Interval
Mitral E velocity (cm/s)	66.2 ± 4.3	57.4, 74.9
Septal e' (cm/s)	10.6 ± 13.9	6.1, 15.1
Lateral e' (cm/s)	10.6 ± 3.3	9.5, 11.6
E-e' ratio	8.5 ± 3.3	7.5, 9.6
E-A ratio	1.6 ± 1.5	1.0, 2.1
Diastolic dysfunction	14 (34%)	

Table 5.5 showing LA echocardiographic diastolic parameters in all patients. Data presented in mean ± standard deviation or n (%).

Table 5.6: Echocardiographic markers of diastolic parameters comparing different AF Phenogroups.

LA functional measures	AF Phenogroup 1	95% Confidence Interval	AF Phenogroup 2	95% Confidence Interval	P-value
Mitral E velocity (cm/s)	60.8 ± 21.1	48.6, 73.0	69.3 ± 29.2	56.9, 81.6	0.35
Septal e' (cm/s)	7.3 ± 1.5	6.4, 8.2	12.5 ± 17.0	5.4, 19.7	0.26
Lateral e' (cm/s)	11.0 ± 2.3	9.7, 12.3	10.2 ± 3.7	8.7, 11.8	0.51
E-e' ratio	7.9 ± 2.3	6.6, 9.3	8.9 ± 3.6	7.3, 10.4	0.39
E-A ratio	1.3 ± 0.3	1.0, 1.5	1.7 ± 1.8	0.9, 2.6	0.42
Diastolic dysfunction	2 (13)		12 (48)		0.035

Diagnosis of diastolic dysfunction is made according to JASE guidelines 2016. Data presented in mean ± standard deviation or n (%).

Table 5.7. Echocardiographic evidence of LA and LV structural remodelling, as binary variables, analysed by AF Phenogroups.

Echocardiographic measures	AF Phenogroup 1	AF Phenogroup 2	P-value
LA dysfunction †	5 (35.7)	16 (64)	0.06
LA enlargement † †	2 (18.2)	15 (62.5)	0.015
LA dysfunction and enlargement ¥	1 (9.1)	13 (54.2)	0.012
LV subclinical systolic dysfunction ¥¥	4 (36.4)	13 (59)	0.2

Table 5.7 showing the proportion of patient in each AF phenogroups with evidence of adverse echocardiographic markers of LA and LV structural and functional remodelling. Data presented in n (%).

† LA dysfunction is defined as LA ejection fraction less than 45%.

† † LA enlargement is defined as indexed LA volume > 40 ml^3/m^2.

¥ LV subclinical systolic dysfunction is defined as LV GLS > -17.

¥ ¥ LA dysfunction and enlargement include AF patients with both evidence of enlarged LA (indexed LA volume > 40 ml^3/m^2) and LA dysfunction (LA ejection fraction less than 45%).

5.8 Figures

Figure 5.1: Echocardiographic assessment of LA functional remodelling

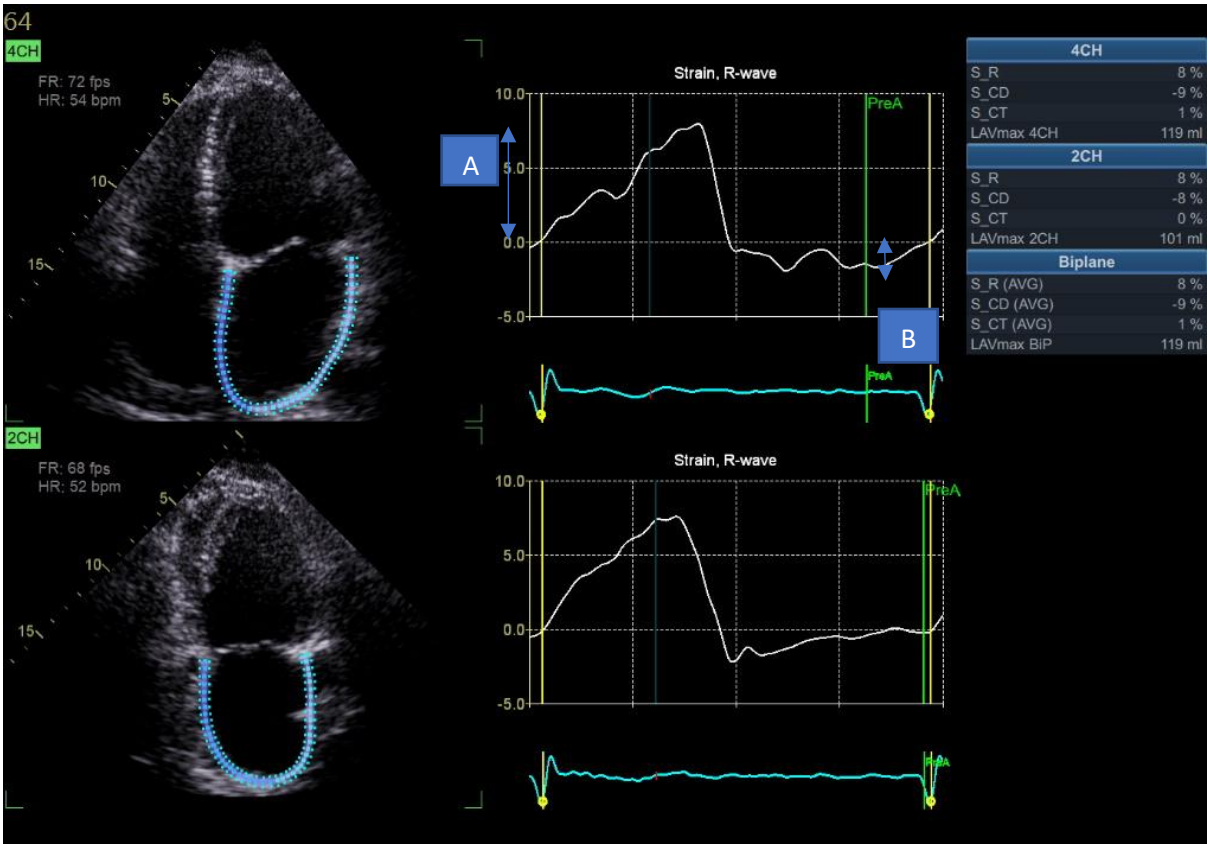


Figure 5.1 showing on 1) Left panel: Tracking of the LA endocardium in apical 4 chamber and apical 2 chamber and 2) Right hand panel: Using QRS as reference point, tracking of the LA endocardium movement throughout LA filling, diastasis and contraction allows the calculation of corresponding LA reservoir, conduit and contractile function. LA phasic results in biplane mode were used for this study.

When patient is in AF, only LA reservoir (A) and LA conduit (B) was available for measurements.

Chapter 6

Role of the right atrium in atrial fibrillation. Electrophysiological insights from renewal theory-based fibrillatory dynamic analysis.

6.1 Abstract

Background: The role of the right atrium (RA) in AF remains poorly understood. We have recently shown that electrophysiological assessment of fibrillatory dynamics may be performed using renewal theory, where the formation and destruction of phase singularities (PS) converge to a constant stable state and are associated with adverse clinical outcomes following pulmonary vein isolation (PVI). Using the renewal approach, we seek to understand fibrillatory dynamics in the RA, and explore the associations between renewal theory with atrial remodelling and clinical outcomes post AF ablation.

Methods: RENEWAL-AF was a prospective multicentre observational study recruiting AF ablation patients. Unipolar electrograms were obtained from six pre-defined RA locations using 16-electrode Advisor TM HD-Grid catheter. Renewal rate constants λ_f, and λ_d for each RA location were determined.

Results: N=48 patients, 28.5% females were recruited. λ_f and λ_d in all regions were highly correlated. Rho (ρ) values (λ_f/λ_d), defined as the average PS formed per unit time was calculated. The highest ρ (average rotor formed per unit time, ratio of λ_f to λ_d) was observed in the RA appendage. Two groups were analysed: Group 0 (negative LA to RA ρ gradient) and Group 1 (positive LA to RA ρ gradient). Group 0 was associated with a significantly reduced RA phasic function and was closely related to AF Phenogroup (P=0.07). After six-months, a higher AF burden (hours) was observed in Group 0 (P=0.02). On multivariate

regression analysis, AF Phenogroup was the only significant predictor of loss of LA to RA ρ gradient (P=0.019).

Conclusion: Electrophysiologic assessment of the RA using renewal theory showed significant associations with RA functional remodelling and was associated with poor prognostic markers post AF ablation.

6.2 Introduction

While the role of left atrium (LA) in atrial fibrillation (AF) persistence has been well established, the role of the right atrium (RA) in the initiation and maintenance of AF remains poorly understood. It has been suggested that a specific subset of AF patients clinically respond to selective RA substrate modification without pulmonary vein isolation (PVI) (187). Supporting this is the observation that freedom from atrial tachyarrhythmias recurrence is up to 80% in patients who undergo surgical treatment of AF, the Cox Maze 4 procedure which multiple RA lesions in addition to LA lesion sets and surgical excision of the left atrial appendage (658, 659). However, clinical outcomes from selective RA catheter ablation as an adjunct to pulmonary vein isolation (PVI) have been equivocal (660-662). A potential reason for this is an inadequate electrophysiological characterisation of AF patients, resulting in suboptimal selection of AF patients who would clinically benefit from adjunctive RA substrate modification strategy.

An emerging method for fibrillatory dynamic analysis in human fibrillation is by using a statistical approach, the renewal theory (16, 457, 472, 520, 564). This is based on the on common observations that spiral wave lifetimes in AF were exponentially distributed (431, 460, 461, 463, 464), similar to that of spiral wave lifetimes and distribution from other spatiotemporally turbulent systems in other biological systems (525, 528). Further, we have recently shown that electrophysiologic classification of AF patients using the renewal approach was associated with improved clinical outcomes in AF patients who a PVI-only ablation. In this study, we aim to explore the electrophysiologic characteristics of fibrillatory dynamics in the RA and their relationship to RA structural and functional remodelling, and clinical outcomes post AF ablation.

6.3 Methods

Study population

RENEWAL-AF (ACTRN 12619001172190p) was a prospective multicentre observational study involving four Australian sites, which included n=48 AF patients who had clinical indications for AF ablation and referred for an AF ablation procedure (31).

Transthoracic echocardiogram

Transthoracic echocardiogram (TTE) was performed in all patients using a Vivid E95 ultrasound system. All measurements were made according to the American Society of Cardiology Guidelines (269). Right atrial (RA) volume and area were measured from focused right sided views on the apical four chamber view. Right atrial (RA) volume and area were measured from focused right sided views on the apical four chamber view. RA area was measured at the end of systole while RA volume index was obtained using the Simpsons method in the apical four chamber view, indexed to body surface area. RA endocardial speckle tracking was performed from the apical four chamber in the RA using Q-analysis (EchoPac Version 202, GE Vingmet Ultrasound) (Figure 6.1). Studies deemed inadequate for analysis and excluded when any part of the tracking is unable to follow the endocardial border completely. RA reservoir, conduit, contractile function along with RA ejection fraction will be determined using the EACVI/ASE/Industry Task Force recommendations to standardize deformation imaging (269).

Electrophysiology study

Patients were mapped under spontaneous or induced AF using the Ensite Precision electroanatomic mapping system (Abbott Cardiovascular, Plymouth MN). Electrograms and ECG were recorded at 1000 Hz, and unipolar electrogram filter band pass was set at 0.5-500 Hz. Sequential one-minute recordings of unipolar and bipolar electrograms were obtained using the Advisor^{TM} HD-Grid catheter (16 electrodes in a square grid catheter 13x13mm^2 grid, 3mm interelectrode-spacing, Abbott Cardiovascular, Plymouth MN) from six pre-defined RA intracardiac locations; 1) Superior vena cava (SVC) – RA junction 2) RA appendage 3) RA septal region 4) RA posterior region 5) RA lateral region 6) RA cavotricuspid isthmus

region. Stability between catheter and RA endocardium were maintained throughout recordings through visualisation of deformation of the HD-Grid catheter on RA endocardial border and presence of sharp local electrograms on the tracings. All AF patients received a PVI-only procedure.

Signal processing

Unipolar electrogram signals were exported and processed as described previously (447, 457, 472). Sinusoidal recomposition was applied with the dominant frequency set as the wavelet period and phase computed using the Hilbert transform to construct phase maps (82, 447, 457, 472). In each phase map, phase singularities (PS) were detected and tracked as previously described using a convolution kernel method based on topological charge (447, 457, 472). PS tracking enabled calculation of PS lifetimes and inter-formation times (times between consecutive PS formations), which also enabled construction of PS lifetime and inter-formation time distributions (447, 457, 472). PS distributions were fitted using maximum likelihood fitting to estimate the rate of PS formation (denoted as λ_f) and PS destruction (λ_d) (447, 457, 472). "ρ" pronounced rho, is the average rotor formed per unit time and is obtained by dividing λ_f / λ_d.

Follow up

All patients enrolled in RENEWAL-AF received a non-invasive Alivecor mobile phone application (app) post AF ablation to monitor AF burden and time to atrial tachyarrhythmia recurrence (days). An increasingly utilised method to assess AF control is by the measurement of AF burden. A sub-study from the STAR-AF 2 trial showed that a greater reduction in AF burden translated to a significantly improved quality of life (589). In patients post AF-ablation, AF burden has been used as a surrogate to assess efficacy of different strategies of catheter ablation (590). More recently, Voskoboinik et al also utilised AF burden, measured twice daily using the AliveCor monitor to measure the influence of alcohol abstinence on AF (414). The method proposed by Voskoboinik et al laid the foundation for the approach used to measure AF burden

in RENEWAL-AF. Similar method for estimation of arrhythmia recurrence and quantification of AF burden post AF ablation was used in the more recently published CAPLA clinical trial (109). Patients were instructed to transmit twice daily 30 second single lead electrocardiogram recordings from Alivecor monitor regardless of symptoms, for a total duration of six months. Additionally, if they had symptoms of AF, patients were asked to transmit a tracing at AF onset and offset of symptoms, so that an estimate AF duration could be made. Atrial tachyarrhythmia recurrence is defined as atrial tachyarrhythmia lasting for ≥ 30 seconds, while time to atrial tachyarrhythmia recurrence is determined from the Alivecor cardiac monitor. In patients not on Alivecor cardiac monitor, first documented atrial tachyarrhythmia recurrence was made using ECG tracings during patient contact in outpatient clinic. All tracings from ECG or Alivecor monitor were reviewed by two cardiologists, blinded to the patient's clinical subgroup classification. At the end of six months, the following clinical endpoints were measured in clinic or via telephone: Recurrence of atrial tachyarrhythmia, AF-related hospitalisations, requirement for cardioversion for AF, need for repeat ablation procedure for atrial tachyarrhythmia and need for intensification of antiarrhythmic therapy. In patients on Alivecor monitor, total AF burden (hours) was calculated. Operators and treating physicians were blinded to the AF Phenogroup status of their patients throughout the entirety of study period.

Statistical analysis

Data normality was checked using the Shapiro Wilk test. Categorical variables were presented as n (%) and differences between groups were examined using the χ^2 test. Continuous variables were analysed using student t test or Wilcoxon-rank sum test, where appropriate. ρ" pronounced rho was calculated and is the average rotor formed per unit time. This is obtained by dividing λ_f / λ_d. Differences between ρ values between different atrial regions were analysed using one-way ANNOVA, followed by Bonferroni correction. Kaplan Meier curve and log-rank test were used to compare freedom from atrial tachyarrhythmia between patients with (Group 1) and without (Group 0) an LA to RA ρ gradient.

In univariate and multivariate analysis, the presence of an LA to RA ρ gradient was used as the main outcome variable while clinical variables (AF Phenogroup, CHA_2DS_2-VASc score, OSA, AF persistence and alcohol intake) and echocardiographic parameters (LV dysfunction, defined as LV ejection fraction ≤ 50%, LA dysfunction, defined as LA ejection fraction of ≤ 45%, LA enlargement, defined as indexed LA volume of ≥ 40 ml/m^2 and RA enlargement, defined as indexed RA volume of ≥ 19 ml/m^2 in females and ≥ 22 ml/m^2 in males (663)) were used as the input variables. Results were reported as regression slope (β) and level of significance. Statistical analysis was performed using STATA version 15.1 with the level of significance set at $P<0.05$.

6.4 Results

Patient baseline characteristics Out of n=48 patients recruited, n=41 patients' data had complete LA recordings for renewal rate constant analysis. N=7 patients were excluded due to inability to induce AF (n=3), hemodynamic instability (n=2), frequent AF termination (n=1) and atypical atrial flutter (n=1). The mean age (years) was 59.5(95% CI 36 - 77), 28.5% females, BMI (kg/m^2) 31.3 (95% CI 29.9 - 32.5) and the median CHA_2DS_2-VASC score was 1 [IQR 1-3]. The measured mean indexed RA end systolic volume was 28.6 (95%CI 25.9-31.3) ml/m^2, the mean RA area was 20.3 (95% CI 19.1-21.6) cm^2 (Table 6.1). Functionally, the measured mean RA ejection fraction (%) was 41.1 (95% CI 35.9 – 46.3), median RA conduit (%) was -16.6 [95% CI -18.8, -14.5], median RA contractile (%) was -11 [IQR -15, -1], and the mean RA reservoir (%) was 25.6 (95% CI 21.4, 29.9) (Table 6.1).

Spatial distribution of ρ in the RA

Similar to the LA, in all sampled RA locations, we observed a high correlation between λ_f and λ_d, with $R^2>0.9$. (Table 6.2). The highest ρ value was observed in the RAA with a mean ρ value of 1.34 (95% CI 1.24, 1.45) while the lowest ρ value was observed in the cavotricuspid isthmus with a mean ρ value of 1.18 (95%

CI 1.15, 1.21) (Figure 6.2) (Table 6.3). Only the ρ value of the RAA was observed to be significantly higher than CTI region (P=0.021) (Figure 6.2).

Association between loss of LA to RA gradient with atrial remodelling, and clinical outcomes

In chapter 3, we observed associations between the loss of PV-LA gradient with adverse clinical outcomes after PVI-only procedure. In chapter 5, we further observed associations between the presence of LA structural and functional remodelling with loss of PV-LA gradient. Previous studies have also observed links between loss of AF cycle length gradient and dominant frequency LA-RA gradient with AF patients who had improved clinical outcomes after additional RA ablation (192, 198).

In this chapter, we analysed the patients according to two groups

1) Group 0: Negative LA to RA ρ gradient (Higher mean ρ in the RA compared to the LA)

2) Group 1: Positive LA to RA ρ gradient (Higher mean ρ in the LA compared to the RA)

The rationale for this analysis was based on previous studies suggesting the role of RA in perpetuation and maintenance of AF in a subgroup of persistent AF patients (184, 664, 665). Further supporting this notion is the finding of RA structural remodelling in persistent AF patients, which has also been shown to predict recurrences post AF ablation (666). Using the renewal approach, quantification of PS formation and destruction using the renewal approach, λ_f and λ_d allows the estimation of average rotor formation per unit time, ρ (λ_f / λ_d) in both LA and RA chambers. We hypothesise that AF patients with a negative left to right atrial ρ gradient (Group 0, with higher mean ρ in the RA compared to the LA) would have evidence of significant echocardiographic evidence of RA structural and functional remodelling with worst clinical outcomes after PVI-only ablation. Further, this could also represent a subset of AF patients who would clinically benefit from additional RA ablation.

Patient baseline characteristics, according to presence or absence of LA to RA gradient

There was n=21(52.5%) patients in Group 0 and n=19(47.5%) patients in Group 1. Mean age (years) between both groups was 58.9 ± 9.5 versus 59.2 ± 2.2, P=0.9, mean BMI (kg/m^2) was 31.8 ± 1.2 versus 31.0 ± 0.8, P=0.5 and the mean CHA_2DS_2-VASc score was 1.8 ± 1.4 versus 2 ± 1.7, P=0.7, respectively (Table 6.1).

Structurally, no significant differences were observed in the indexed RA end-systolic volume (ml^3/m^2) and RA area (m^2) between Group 1 and Group 0 (28.3 ± 8.8 versus 29.2 ± 8.3, P=0.76 and 20.2 ± 3.6 versus 20.8 ± 3.7, P=0.64, respectively). However, we observed that the RA reservoir function (%), RA conduit function (%) and RA contractile function (%) were significantly lower in Group 0 when compared to Group 1 (20.8 ± 8.8 versus 31.5 ± 10.5, P=0.005; -14.6 ± 4.7 versus -18.7 ± 5.8, P=0.04; -6.2 ± 6.4 versus -12.6 ± 6.8, P=0.01, respectively) (Table 6.1).

Spatial distribution of ρ in the RA, analysed by the presence or absence of LA-RA ρ gradient: -

In Group 0, we observed the highest mean ρ value of 1.44 ± 0.4 in the RAA while the lowest ρ value was observed in the cavotricuspid isthmus with a mean ρ value of 1.18 ± 0.06 (Figure 6.3). No significant differences were observed between RA locations in Group 0 (P=0.1).

In Group 1, we observed the highest mean ρ value of 1.24 ± 0.15 in the RAA while the lowest ρ value was observed in the SVC-RA junction with a mean ρ value of 1.13 ± 0.14 (Figure 6.3). No significant differences were observed between RA locations in Group 1 (P=0.091).

Relationship between LA-RA *ρ* gradient, AF Phenogroup and clinical outcomes post AF ablation

When AF Phenogroup 1 patients were compared to AF Phenogroup 2, no significant differences were observed between echocardiographic markers of RA structural and functional remodelling (Table 6.4 and Table 6.5).

9 out of 19 (47%) AF patients with a positive LA to RA ρ gradient were classified as AF Phenogroup 2. However, a non-significantly higher number of AF patients with a negative LA to RA ρ gradient were classified as AF Phenogroup 2 (16 out of 21 AF patients (76.2%), P=0.06) (Table 6.6).

AF burden was significantly higher in patients with a negative LA to RA ρ gradient, when compared to patients with a positive LA to RA ρ gradient (median duration of 38 hours [IQR 0-240] versus median duration of 0 hours [IQR 0-23 hours], P=0.04) (Table 6.7). The presence of LA to RA ρ gradient was not predictive of AF recurrence (P=0.15), re-do ablation procedures (P=0.63), requirement for cardioversion (P=0.29), AF-related hospitalisations (P=0.7) or requirement for intensification of antiarrhythmic therapy (P=0.4) (Table 6.7). Additionally, no difference in time to atrial tachyarrhythmia recurrence was observed between Group 0 patients (negative LA to RA ρ gradient), and Group 1 patients (positive LA to RA ρ gradient) (HR 0.49, 95% CI 0.2-1.2, P=0.12) (Figure 6.4).

Clinical and echocardiographic predictors of the presence or absence of LA to RA ρ gradient

In univariate regression analysis using the presence of LA to RA ρ gradient as a binary variable, AF Phenogroup classification was a non-significant predictor of the presence or absence of LA to RA ρ gradient (P=0.06) (Table 6.8). All measured echocardiographic parameters of LA and RA structural and functional parameters did not meet significance. In multivariate regression analysis, only AF Phenogroup was the significant predictor of the presence of LA to RA ρ gradient (P=0.019) (Table 6.8).

6.5 Discussion

RENEWAL-AF was a multicentre prospective observational study that recruited AF patients undergoing ablation, to investigate the mechanistic and clinical significance of spatial distribution of renewal rate constants in the RA. We hypothesised that a negative LA to RA ρ gradient was a marker of adverse clinical outcomes in AF patients undergoing ablation. Using renewal theory, we observed a significant association between a negative LA to RA ρ gradient with adverse echocardiographic markers of RA functional

remodelling. Clinically, a negative LA to RA ρ gradient was associated with a higher AF burden post-AF ablation. The fact that in some cases the highest renewal rate constants observed in the RAA is of unclear clinical significance, which could be due to the complex musculature of the RAA itself, presence of interatrial communications between the LA and RA structures (such as the Bachmann's bundle) or potentially the role of RAA in the maintenance of AF.

Electrophysiologic characterisation of human AF using renewal theory

Electrophysiologic characterisation of AF patients using the renewal theory is a new quantitative method for fibrillatory dynamics, based on a branch of probabilistic theory in statistics. In our previous studies, we validated the use of the renewal approach in computational and animal models of AF, human AF, and human models of VF. Clinically, we have also shown that in AF patients who underwent PVI-only ablation, characterisation of AF patients using renewal theory was associated with adverse clinical outcomes six months post-AF ablation.

Findings from this study further lend further support to that from our previous studies. Similar to the LA, we observed a high correlation between λ_f and λ_d in all RA regions sampled, suggesting that AF is maintained by continuous regeneration of PS. An exponential distribution of PS lifetimes and inter-formation times was also observed in the RA, a characteristic finding of a system displaying a renewal process. Further, the exponential distribution of the PS lifetimes and formation times imply that AF consists mainly of transient, short-lasting re-entrant circuits. While some studies have suggested a dominant mother rotor driving fibrillation in AF, findings from our study suggest otherwise, that longer-lasting re-entrant circuits were present in all sampled RA regions because of the exponential nature of PS lifetimes.

Role of atrial remodelling in AF persistence

The presence of echocardiographic markers of RA functional remodelling has been linked to the development of AF. In n=142 patients who underwent coronary artery bypass graft, both indexed RA volume and RA reservoir strain were independently associated with the development of post-operative AF (667). In a prospective study involving n=73 patients with atrial septal defect (ASD) who underwent ASD occlude insertion, the combined use of both echocardiographically measured RA expansion index and RA time to peak strain showed a high predictive value for AF development after six months with an area under the curve of 0.9 (668). However, findings from one study have suggested RA structural remodelling may play a more crucial role in AF development, rather than RA functional remodelling. In a prospective study involving n=3147 participants of the Multi-Ethnic Study of Atherosclerosis, Xie et al observed an independent association between CMR-measured minimum (HR 1.12, P=0.037) and maximum indexed RA volume (HR 1.13, P=0.041) with incident AF, but no associations between CMR-derived indices of RA dysfunction and AF, after adjustment for traditional cardiovascular risk factors (183). Another prospective study involving n=30 paroxysmal AF patients recruited from cardiology clinic and then followed up for one year, showed that RA contractile strain was significantly impaired in patients with recurrent AF when compared to patients who remained in sinus rhythm. In addition, a higher RA contractile strain was also linked to sinus rhythm maintenance after 12 months of follow up (669).

In our study, we observed that RA reservoir, conduit and contractile function were significantly lower in AF patients with a negative LA-RA gradient, compared to AF patients with an LA-RA gradient. RA reservoir has previously been shown to correlate with RA pressures. In a recently published study by Miah et al involving n=103 heart failure patients who underwent both echocardiographic RA strain quantification and right heart catheterisation, reduced RA reservoir independently predicted elevated RA pressure (defined as mean RA pressure>7 mm Hg) with improved diagnostic performance to performance to conventional echocardiographic methods – inferior vena cava size and collapsibility and RA size (670).

Similar associations between RA reservoir and RA pressure have been observed in patients with pulmonary hypertension (671, 672).

Despite significantly lower RA phasic strain parameters in patients with a negative LA to RA gradient, we observed no significant differences between the RA area and indexed RA end-systolic volume in both AF Groups. A potential reason for this is that RA function is a highly sensitive marker for RA pressure and/or volume overload (673) and it is plausible that most patients included in this study have RA dysfunction without RA enlargement.

Role of RAA in AF: Mechanistic insights and clinical implications

In our study, we observed the highest ρ in the RAA in all patients and when analysed by the presence or absence of LA to RA gradient. The RAA is a triangular-shaped cardiac outpouching located on the RA anterior wall comprised of multiple endocardial longitudinal and perpendicular muscular fascicles (674). Structurally, it has been observed that RAA volume is larger in AF patients than in patients without AF using trans-esophageal echocardiography (675). Histologically, increased amounts of fibrofatty infiltration of the RAA have been observed, specifically in older patients and patients with persistent AF on RA appendage samples taken from n=92 patients who underwent cardiac surgery (676). Anatomically, RAA is also closely connected to the LA, specifically the LAA through Bachmann's bundle (150). Findings from the limited prospective and retrospective analysis have suggested that there may be clinical benefit from targeted RAA ablation. Ghannam et al showed that in n=113 persistent AF patients who underwent RAA ablation, when a right-to-left AF cycle length gradient was present, 78% of patients remained free from arrhythmia recurrence after 24 months follow up (677). Another retrospective study by Liu et al showed that in a subset of AF patients with high frequency potentials in the RAA, AF could be terminated acutely after catheter ablation at the base of the RAA or by mechanical stimulation of the RAA (490).

Loss of left to right dominant frequency or AF cycle length gradient as a predictor of clinical response to additional RA ablation.

Previous studies have suggested that either the presence of either an AF cycle length gradient or a dominant frequency gradient (left-to-right versus right-to-left gradient) will help determine a patient's clinical response to LA only ablation or LA with additional RA ablation.

a. In a study by Hocini et al involving n=148 persistent AF patients, a parallel increase in biatrial AF cycle length during LA only ablation predicted excellent clinical outcomes after 40 months follow up. However, in 30% (n=44) patients with a right to left AF cycle length gradient after LA ablation, AF cycle length prolongation in the RA with adjunct RA substrate modification particularly around the region of RAA, anterior RA and lateral RA significantly predicted improved clinical outcomes compared to patients without a cycle length change during RA ablation. Further atrial structural characterisation revealed the presence of enlarged RA size in AF patients with a right to left AF cycle length gradient. Findings from this study suggest a subset of patients with electrophysiologically significant RA substrate that may clinically respond to additional RA ablation (194).

b. In a prospective study involving n=27 AF patients (n=15 paroxysmal AF and n=12 persistent AF patients), Lazar et al observed that the presence of left to right dominant frequency gradient, particularly in persistent AF patients predicted longer freedom from atrial tachyarrhythmias from a PVI-only procedure, when compared to persistent AF patients without a left to right dominant frequency gradient (192).

Concept of AF as a biatrial disease: Role of the RA

While the role of the LA remodelling in AF is well established, the role of RA remodelling in AF initiation and maintenance is less clear. A previous study has suggested that atrial remodelling in AF in fact, occurs in both atria, rather than in the LA specifically. In n=40 persistent AF patients who underwent biatrial

electroanatomical mapping prior to catheter ablation, a significant degree of correlation was observed between conduction velocity (R = 0.49, P = 0.001), electrogram fractionation (R = 0.73, P <0.001), and bipolar voltage (R = 0.57, P <0.001) in the LA and RA (678). In addition, no significant differences were observed between the mean global bipolar voltage (P=0.57), complex electrograms (P=0.99) or low voltage areas (P=0.84) in both chambers (678). Findings from this study suggest that remodelling in AF is a biatrial process, rather than a specific atrial disease affecting the LA.

Histological analysis from human atrial tissue samples have shown significantly higher degrees of fibrosis and apoptotic burdens in atrium which exhibits impaired atrial mechanical function, specifically, reserve, contractile and conduit strain, suggesting a mechanistic link between impaired atrial function with fibrotic, and diseased atrium (679). Further, another study has observed increased susceptibility of AF induction in animal models of RA enlargement. In rats with monocrotaline-induced pulmonary hypertension, increased right ventricular pressure and mass was observed, along with right atrial enlargement. AF was induced in 100% (32 out of 32) of rat models with pulmonary hypertension compared to 6% (2 out of 32) controls (179). Optical mapping showed conduction slowing and stable rotors in rat models with RA remodelling while transcriptomic analysis showed increased genetic predisposition for inflammation, hypertrophy and fibrosis (179).

Previous studies have demonstrated a loss of an LA to RA dominant frequency gradient in persistent AF patients, but not in paroxysmal AF (192). In our study, we observed a trend towards significance between AF Phenogroup 2, patients with highest rho value in the LA body with a loss of LA to RA gradient. While pulmonary vein triggers have been postulated to play a crucial role in AF initiation, it is likely that as AF persists, electrical, functional, and structural remodelling affects both atria, rather than purely the LA alone. The concept of AF as a biatrial disease has previously been described in the literature. In specific animal models with right heart disease, conduction slowing along with RA fibrosis and enhanced inflammatory, profibrotic and hypertrophic responses have been observed to contribute to increased

susceptibility of AF initiation and maintenance (179). In human studies, immunohistochemical analysis of myocardial biopsies from the LA and RA of n=46 patients undergoing cardiac surgery showed a significantly greater degree of elastin, vascular endothelial growth factor (VEGF) and lower microvascular density in the RA compared to the LA in AF patients (680). In addition, reverse echocardiographic markers of structural and functional remodelling , both in the left and right atria were observed in n=48 AF patients who maintained sinus rhythm six months post electrical cardioversion (681). Importantly, the association between loss of LA to RA ρ gradient and worst clinical outcomes post PVI-only procedure observed in our study identifies a subset of patient less responsive to conventional PVI procedures, which may refine patient selection for additional atrial substrate modification, in addition to PVI.

Limitations

There are a few limitations to this study. Firstly, the relatively small number of patients recruited may have confounded our observation of the lack of RA structural remodelling and the lack of association with AF Phenogroup in patients with negative LA to RA gradient. Secondly, the relatively short duration of follow up may lead to an erroneous observation of a significantly lower AF burden in patients with loss of LA to RA ρ gradient. Finally, the observation of high renewal rate constant in the RAA may be a result of the relatively complex myofiber orientation and architecture in the appendage, when compared to other RA locations sampled. Hence, its role as a passive bystander or an active regional driver for AF in RA remains unclear. Further randomised studies with RAA isolation plus PVI versus PVI alone in non-responders would be required to answer this clinical question.

6.6 Conclusion

In our study, we have further demonstrated the use of renewal theory as a robust quantitative metric in fibrillatory dynamic analysis in the RA in human AF. Mechanistically, renewal theory suggests that AF is maintained by continuous regeneration of re-entrant circuits, which consists predominantly of transient,

short lasting phase singularities. Clinically, the association between worst clinical outcomes post AF ablation with the loss of LA to RA ρ gradient could serve as a prognostic tool for patients who would benefit less from conventional PVI-only approach in AF and further define a subset of patients who would benefit from additional substrate modifications.

6.7 Tables

Table 6.1: Patient baseline characteristics, analysed by the presence or absence of LA-RA ρ gradient.

Baseline Demographics	Mean (SD) or n [%]	Group 0 negative ρ gradient (n=21)	Group 1 positive ρ gradient(n=19)	P-Value
Age (years)	59 (9.5)	58.9 ± 9.5	59.2 ± 2.2	P=0.9
BMI (kg/m^2)	31.4 (4.3)	31.8 ± 1.2	31.0 ± 0.8	P=0.5
Sex, female [%]	11 [27.5]	7 [33.3]	4 [21.1]	P=0.4
Diabetes mellitus [%]	3 [7.5]	3 [14.3]	0 [0]	P=0.09
Hypertension [%]	17 [42.5]	9 [42.9]	8 [42.1]	P=0.96
Vascular disease [%]	8 [20.0]	3 [14.3]	5 [26.3]	P=0.3
Hyperlipidemia [%]	13 [32.5]	7 [33.3]	6 [31.6]	P=0.9
OSA [%]	14 [35]	6 [28.6]	8 [42.1]	P=0.37
Heart failure [%]	17 [42.5]	6 [28.6]	11 [57.9]	P=0.06
CVA [%]	6 [15]	3 [14.3]	3 [15.8]	P=0.89
Smoking history [%]	10 [25]	6 [28.6]	8 [42.1]	P=0.58
Alcohol intake [%]	26 [65]	13 [62]	13 [68.4]	P=0.67
CHA2DS2-VASc score	1 [1-3]	1.8 ± 1.4	2 ± 1.7	P=0.7
Paroxysmal AF [%]	16 [41]	10 [48]	6 [31.2]	P=0.26
AF Phenogroup 1 [%]	15 [37.5]	5 [23.8]	10 [52.6]	P=0.06
RA area (m^2)	20.5 (3.6)	20.2 ± 3.6	20.8 ± 3.7	P=0.64
Indexed RA ESV (ml^3/m^2)	28.7 (8.4)	28.3 ± 8.8	29.2 ± 8.3	P=0.76
RA ejection fraction [%]	41.5 (13.2)	38 ± 13.2	45.4 ± 12.6	P=0.13
RA reservoir [%]	25.8 (10.9)	20.8 ± 8.8	31.5 ± 10.5	P=0.005
RA conduit [%]	-16.5 (5.6)	-14.6 ± 4.7	-18.7 ± 5.8	P=0.04
RA contractile [%]	-9.2 (7.3)	-6.2 ± 6.4	-12.6 ± 6.8	P=0.01

Data presented as mean (standard deviation), or n [%]

Table 6.2: Degree of correlation between λ_f and λ_d depending on specific RA location.

RA Location	P-value	R^2 value
SVC-RA junction	P<0.001	0.94
RAA	P<0.001	0.98
RA Posterior	P<0.001	0.98
RA Lateral	P<0.001	0.98
RA septal	P<0.001	0.97
CTI RA junction	P<0.001	0.98

Data presented as strength of correlation, R^2 value and associated P-values.

Table 6.3: Spatial distribution of highest ρ values in the RA.

RA Locations	N (%)
SVC-RA junction	3 (7.5)
RAA	16 (40)
RA Posterior	5 (12.5)
RA Lateral	9 (22.5)
RA Septal	3 (7.5)
Cavotricuspid isthmus	4 (10)

Data presented in n (%).

Table 6.4: Echocardiographic markers of RA structural remodelling comparing AF Phenogroups.

RA structural measures	AF Phenogroup 1	AF Phenogroup 2	P-values
RA area (cm^2)	21.3 ± 3.8	20.4 ± 3.5	0.5
RA end systolic volume (ml^3)	64.9 ± 20.7	61.3 ± 17.8	0.59
Indexed RA end systolic volume (ml^3/m^2)	29.5 ± 9.1	29.0 ± 7.7	0.85

Table 6.4 showing RA structural echocardiographic measures comparing AF Phenogroups. Data presented as mean ± standard deviation.

Table 6.5: Echocardiographic markers of RA functional remodelling comparing AF Phenogroups.

RA functional measures	All patients	AF Phenogroup 1	AF Phenogroup 2	P-values
RA ejection fraction	42.1 ± 13.2	46.3 ± 15.6	39.6 ± 11.2	0.16
RA conduit	-16.7 ± 5.5	-17.3 ± 6.6	-16.3 ± 5.7	0.64
RA reservoir	26.6 ± 11.1	29 ± 12.7	25.1 ± 10.0	0.34
RA contractile	-9.8 ± 7.4	-11.5 ± 8.4	-8.7 ± 6.8	0.31

Table 6.5 showing RA functional echocardiographic measures comparing AF Phenogroups. Data presented as mean ± standard deviation.

Table 6.6: Association between AF Phenogroups and presence or absence of LA to RA gradient

Electrophysiological classification	AF Phenogroup 1 (n=15)	AF Phenogroup 2 (n=25)	Total
Group 0 (Negative LA to RA ρ gradient) (n=21)	5	16	21
Group 1 (Positive LA to RA ρ gradient) (n=19)	10	9	19
Total	15	25	40

Table 6.6 showing the distribution and numbers of AF patients when classified into AF Phenogroups and depending on presence (Group 1) or absence (Group 0) of LA to RA ρ gradient.

Table 6.7: Clinical outcomes of AF Patients, when analysed by the presence or absence of LA to RA gradient.

Clinical outcomes measured	Group 0 (n=20)	Group 1 (n=19)	P-value
Atrial tachyarrhythmia recurrence, n [%]	13 [65]	8 [42.1]	0.15
Atrial tachyarrhythmia burden on Alivecor (hours)	38 (0, 240)	0 (0, 23)	0.04
Escalation in antiarrhythmic therapy	5 [25]	3 [15.8]	0.4
Electrical cardioversion	3 [15]	1 [5.3]	0.29
Atrial fibrillation, atrial flutter and/or atrial tachycardia ablation	3 [15]	2 [10.5]	0.63
AF-related hospitalisation	4 [21]	5 [26.3]	0.7

Data presented as n [%], median (IQR), median (IQR) or mean ± standard deviation. AF recurrence is defined as AF documented on 12-lead surface ECG or single lead Alivecor cardiac monitor.

Table 6.8: Clinical and echocardiographic predictors of presence or absence of LA to RA ρ gradient.

Variable	Univariate model β, 95% CI	P-value	Multivariate model β, 95% CI	P-value
Persistent AF	0.16 (-0.16, 0.5)	0.31		
AF Phenogroup	-0.31 (-0.63, 0.017)	0.06	0.095 (-0.88, -0.084)	0.019
Obstructive sleep apnea	0.14 (-0.19, 0.49)	0.38		
Alcohol intake	0.07 (-0.27, 0.41)	0.68		
CHA_2DS_2-VASc score	0.02 (-0.03, 0.18)	0.7		
Diastolic dysfunction	-0.23 (-0.57, 0.12)	0.19	-0.48 (-0.28, 0.47)	0.61
RA dysfunction	-0.29 (-0.65, 0.075)	0.11	-0.16 (-0.54, 0.21)	0.37
RA enlargement	-0.27 (-0.72, 0.19)	0.24		
LA enlargement	-0.1 (-0.44, 0.25)	0.56		
LA dysfunction	-0.19 (-0.52, 0.15)	0.27		
LV dysfunction	-0.09 (-0.52, 0.35)	0.69		

Table 6.8 showing univariate and multivariate regression modelling using clinical and echocardiographic variables to predict the of presence of LA to RA gradient. RA dysfunction is defined as RA ejection fraction of ≤ 45%. RA enlargement is defined as indexed RA volume of ≥ 19 ml/m^2 in females and ≥ 22 ml/m^2 in males. LA dysfunction is defined as LA ejection fraction of ≤ 45%. LA enlargement is defined as indexed LA volume of ≥ 40 ml/m^2. LV dysfunction is defined as LV ejection fraction of ≤ 50%.

6.8 Figures

Figure 6.1: RA functional assessment in a patient with AF using RA strain, RA conduit and RA contractile measurements.

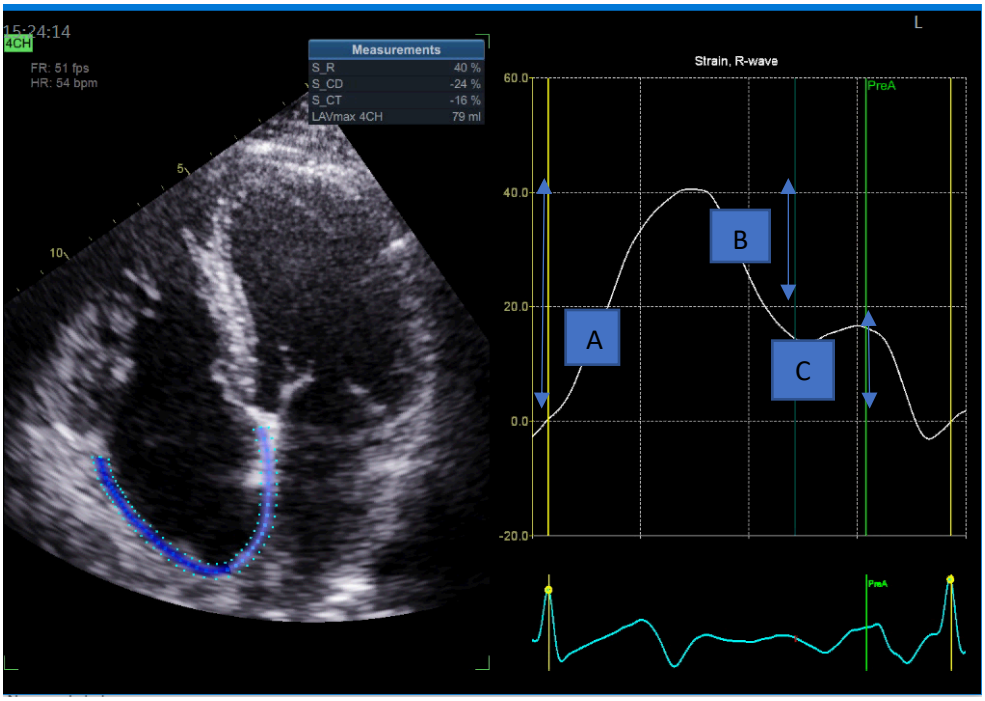


Figure 6.1: RA functional assessment using RA strain. Using R wave as the starting point for RA strain analysis,

a. RA reservoir (A): Occurs from the time of TV closure until the time of TV opening, encompassing time of RV isovolumic contraction, ejection and isovolumic relaxation. RA reservoir strain is the difference between the strain value at TV opening and the RV end diastole.

b. RA conduit (B): RA conduit phase occurs from the time of tricuspid valve (TV) opening until the onset of RA contraction, in patients in sinus rhythm. RA conduit strain is measured as the difference between the strain value at the onset of atrial contraction minus TV opening.

c. RA contractile (C): RA contractile phase occurs from the onset of RA contraction until the end of right ventricular diastole. RA contractile strain is only measured in patients in sinus rhythm at the time of assessment, as the difference of the strain value at the end of RV diastole and the strain value at the onset of atrial contraction.

Figure 6.2: Spatial distribution of ρ in the RA in all patients.

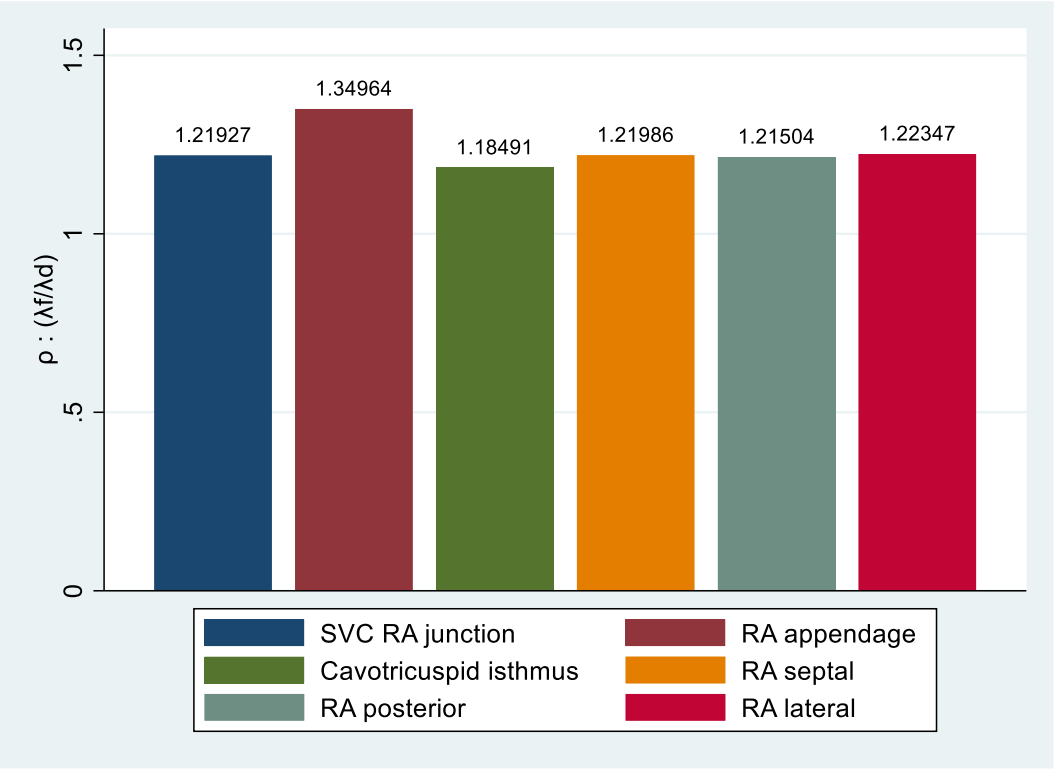


Figure 6.2 showing spatial distribution of mean ρ from six RA locations sampled from all AF patients. The highest ρ value was observed in the RAA with a mean ρ value of 1.34 (95% CI 1.24, 1.45) while the lowest ρ value was observed in the cavotricuspid isthmus with a mean ρ value of 1.18 (95% CI 1.15, 1.21) (Figure 6.2) (Table 6.3). Only the ρ value of the RAA was observed to be significantly higher than CTI region (P=0.021).

Figure 6.3: Spatial distribution of ρ in the RA, when analysed by the presence or absence of LA-RA ρ gradient.

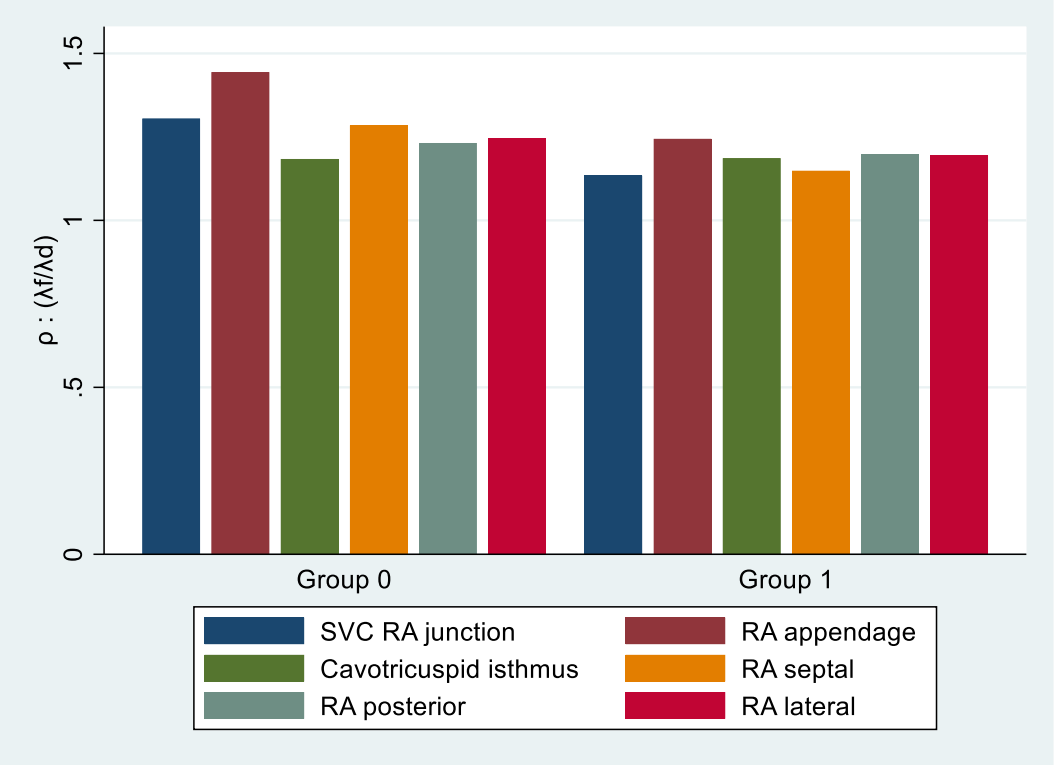


Figure 6.3 showing spatial distribution of mean ρ from six RA locations sampled from AF patients, divided by Group 0 (Negative LA-RA ρ gradient) and Group 1 (Positive LA-RA gradient). In Group 0, we observed the highest mean ρ value of 1.44 ± 0.4 in the RAA while the lowest ρ value was observed in the cavotricuspid isthmus with a mean ρ value of 1.18 ± 0.06. In Group 1, we observed the highest mean ρ value of 1.24 ± 0.15 in the RAA while the lowest ρ value was observed in the SVC-RA junction with a mean ρ value of 1.13 ± 0.14.

Figure 6.4: Time to atrial tachyarrhythmia recurrence, analysed by the presence or absence of LA-RA ρ gradient.

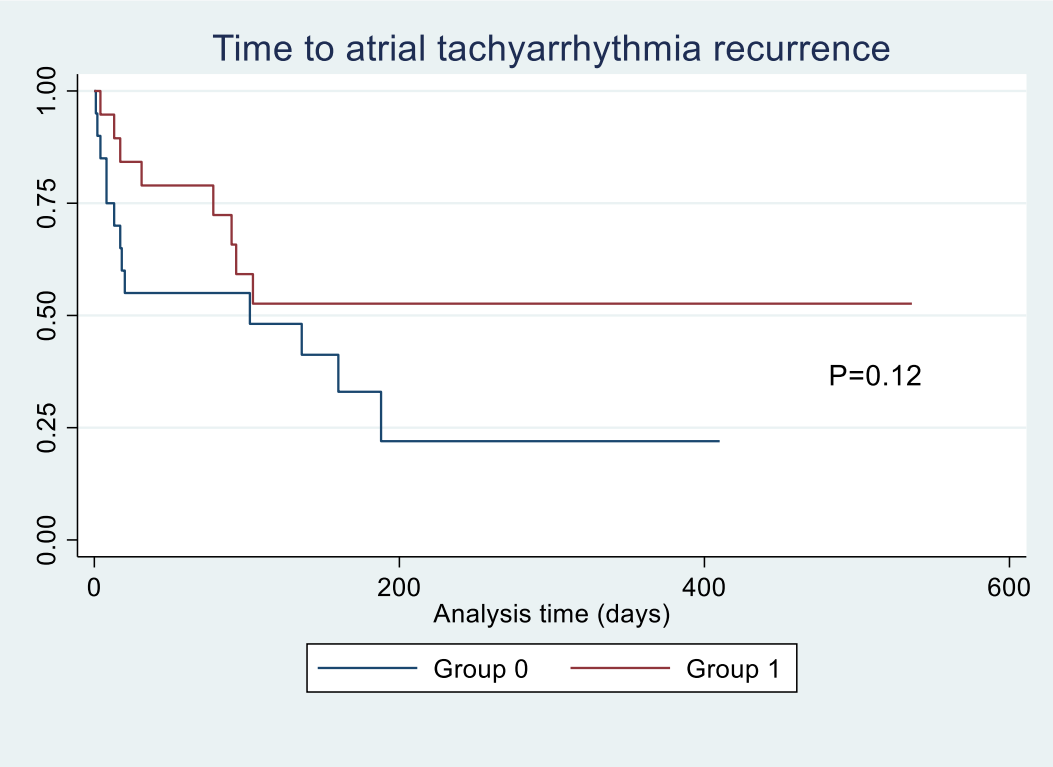


Figure 6.4 showing time to atrial tachyarrhythmia recurrence (days), post PVI-only procedure, analysed by presence (Group 1) or absence (Group 0) of an LA to RA gradient. No difference in time to atrial tachyarrhythmia recurrence was observed between Group 0 patients (negative LA to RA *ρ* gradient), and Group 1 patients (positive LA to RA *ρ* gradient) (HR 0.49, 95% CI 0.2-1.2, P=0.12)

Chapter 7

Relationship between subclinical left ventricular systolic dysfunction and atrial structural, functional, and electrophysiological properties

7.1 Abstract

Background: The co-existence of HF with AF is common and has been associated with adverse cardiovascular outcomes. LV global longitudinal strain (LV GLS) is a sensitive echocardiographic marker of subclinical myocardial dysfunction. In AF, abnormal LV GLS is predictive of new-onset AF and poor clinical outcomes after catheter ablation. Mechanistically, limited studies have explored the electrophysiological, structural, and functional consequences of abnormal LV GLS in the left atrium (LA). In this study, we aim to explore the relationship between AF fibrillatory dynamics, as assessed using the renewal theory, with LA structure and function with abnormal LV GLS.

Methods: RENEWAL-AF is a prospective multicentre observational study recruiting AF ablation patients (ACTRN 12619001172190). Unipolar electrograms were obtained from ten LA locations using a 16-electrode Advisor TM HD-Grid catheter. Renewal rate constants λ_f, λ_d, and the rho (ρ) values (λ_f / λ_d) were calculated. Structural and functional LA assessment and LV GLS analysis were performed pre-ablation in all patients. LV GLS was obtained by obtaining the mean of 18 cardiac segments, from the apical four-chamber, apical three-chamber, and apical two-chamber views.

Results: *Section 1*: Patients with abnormal LV GLS showed evidence of atrial structural and functional remodelling (LAVi (ml/m^2) 38.6 ± 5.5 versus 48.7 ± 9.0, P=0.005; LA ejection fraction (%) 47.7 ± 8.9

versus 30.9 ± 11.5, P<0.001. A higher mean anterior wall ρ was observed in patients with normal LV GLS when compared to abnormal LV GLS (P=0.05).

Section 2: In patients with normal LV EF, abnormal LV GLS was associated with a higher CHA_2DS_2-VASc score (P=0.04), larger LA volume index (P=0.02) and lower LA ejection fraction (%) (P=0.0002).

Section 3: In AF renewal Phenogroup 2 patients, abnormal LV GLS was associated with non-significantly higher AF burden (P=0.068) post AF ablation with a larger LAVi (P=0.002) and lower LA ejection fraction (P<0.001).

Conclusion: The presence of abnormal LV GLS was associated with bi-atrial structural and functional remodelling, even in patients with normal LV EF, and trended towards adverse clinical outcomes post PVI-only procedure.

7.2 Introduction

The presence of AF in patients with both heart failure (HF) with preserved ejection fraction (HFpEF) or HF with reduced ejection fraction (HFrEF) is common and has been linked with negative cardiovascular outcomes (682, 683). Recently, it has been suggested that the prognosis of AF between these HF subtypes may be different. For instance, a recently published prospective observational study involving n=14 694 AF patients with heart failure showed significantly higher rates of HF hospitalisation and combined mortality in patients with HFpEF and HF with mildly reduced ejection fraction (HFmREF), when compared to HFrEF patients (682). Similarly, other reports have demonstrated an increased risk of HF hospitalisation, cardiovascular death, stroke and mortality with HFpEF and AF, when compared to HFrEF patients (684, 685). In these studies, LV function was quantified using echocardiographically using LV ejection fraction (LVEF), which is considered the echocardiographic gold standard for estimation of cardiac function (684, 685). However, major limitations exist with the use of LVEF in terms of its diagnostic and prognostic ability in certain cohorts of patients, specifically in patients with LVEF >40% or with a clinical diagnosis of HFpEF (686-689).

To address this challenge, LV global longitudinal strain (GLS), a metric based on the percentage longitudinal shortening of the ventricle relative to baseline length, has been proposed as a potentially sensitive marker of subclinical myocardial dysfunction (690). Crucially, abnormal LV GLS has been linked to adverse cardiovascular outcomes in patients with LVEF>40% and HFpEF patients, overcoming the limitations of conventional echocardiographic cardiac function estimation using LVEF (691, 692). In AF, the presence of abnormal LV GLS is predictive of both incident AF, while freedom from AF has also been associated with a significant improvement in LV GLS post catheter ablation (693, 694). However, mechanistically, limited evidence to date has explored the association between abnormal LV GLS with AF fibrillatory dynamics, and echocardiographic markers of LA structural and functional remodelling.

Furthermore, to date there has been limited data is available on the effect of CHF on the spatial distribution of fibrillatory dynamics in AF patients. Using optical mapping, Tanaka et al observed, a peripheral distribution of endocardial breakthrough waves in AF distribution, closer to the pulmonary vein ostia in HF animal models, with significantly increased amounts of fibrosis observed on histological analysis resulting in conduction delays, wave breaks and signal fragmentation, compared to control animal models (195).

In this study, we aim to define the fibrillatory dynamics in patients with abnormal LV GLS, and further, investigate the association between markers of structural and functional LA remodelling in these patients.

7.3 Methods

Study population

RENEWAL-AF (ACTRN 12619001172190p) was a prospective multicentre observational study involving four Australian sites, which included n=48 AF patients who had clinical indications for AF ablation (31). Baseline demographics and transthoracic echocardiograms were obtained pre-procedurally.

Echocardiographic measurements

LV global longitudinal strain measurement

Transthoracic echocardiogram (TTE) was performed in all patients using a Vivid E95 ultrasound system before the ablation procedure. All measurements were made according to the American Society of Cardiology Guidelines (269). LV GLS was determined using 2D-standard echocardiography (EchoPac Version 203, GE Vingmet Ultrasound). Three LV apical views were obtained for this purpose, using a frame rate between 60 to 90 frames per second (apical four-chamber views, apical three chamber views and apical two-chamber views). Tracking of the ventricular endocardial border was performed frame by frame throughout the cardiac cycle. Manual adjustment was performed by the operator when tracking of the

endocardial border was inaccurate. Mean GLS was obtained by averaging all 18 ventricular segments. When the patient presented in AF, three cardiac cycles with the most similar R-R interval were chosen for analysis. Studies with poor endocardial border definition, were deemed inadequate for analysis and excluded from the study.

LA structure and function measurement

LA structural and functional assessments were performed as previously described in Chapter 5.

Electrophysiology study

Patients were mapped under spontaneous or induced AF using the Ensite Precision electroanatomic mapping system (Abbott Cardiovascular, Plymouth MN). Electrograms and ECG were recorded at 1000 Hz, and unipolar electrogram filter band pass was set at 0.5-500 Hz. Sequential one-minute recordings of unipolar and bipolar electrograms were obtained using the Advisor^{TM} HD-Grid catheter (16 electrodes in a square grid catheter 13x13mm^2 grid, 3mm interelectrode-spacing, Abbott Cardiovascular, Plymouth MN) from sixteen different intracardiac locations; six RA locations, 1) Superior vena cava (SVC) – RA junction 2) RA appendage 3) RA septal region 4) RA posterior region 5) RA lateral region 6) RA cavotricuspid isthmus region. Stability between catheter and RA endocardium were maintained throughout recordings through visualisation of deformation of the HD-Grid catheter on RA endocardial border and presence of sharp local electrograms on the tracings. All AF patients received a PVI-only procedure.

Signal processing

Unipolar electrogram signals were exported and processed as described previously (447, 457, 472). Sinusoidal recomposition was applied with the dominant frequency set as the wavelet period and phase computed using the Hilbert transform to construct phase maps (82, 447, 457, 472). In each phase map,

phase singularities (PS) were detected and tracked as previously described using a convolution kernel method based on topological charge (447, 457, 472). PS tracking enabled calculation of PS lifetimes and inter-formation times (times between consecutive PS formations), which also enabled construction of PS lifetime and inter-formation time distributions (447, 457, 472). PS distributions were fitted using maximum likelihood fitting to estimate the rate of PS formation (denoted as λ_f) and PS destruction (λ_d) (447, 457, 472). "ρ" pronounced rho, is the average rotor formed per unit time and is obtained by dividing λ_f / λ_d.

Follow up

All patients enrolled in RENEWAL-AF received a non-invasive Alivecor mobile phone application (app) post AF ablation to monitor AF burden and time to atrial tachyarrhythmia recurrence (days). An increasingly utilised method to assess AF control is the measurement of AF burden. A sub-study from the STAR-AF 2 trial showed that a greater reduction in AF burden translated to a significantly improved quality of life (589). In patients post AF-ablation, AF burden has been used as a surrogate to assess the efficacy of different strategies of catheter ablation (590). More recently, Voskoboinik et al also utilised AF burden, measured twice daily using the AliveCor monitor to measure the influence of alcohol abstinence on AF (414). The method proposed by Voskoboinik et al laid the foundation for the approach used to measure AF burden in RENEWAL-AF. Patients were instructed to transmit twice daily 30-second single lead electrocardiogram recordings from Alivecor monitor regardless of symptoms, for a total duration of six months. Additionally, if they had symptoms of AF, patients were asked to transmit a tracing at AF onset and offset of symptoms, so that an estimate of AF duration could be made. Atrial tachyarrhythmia recurrence is defined as atrial tachyarrhythmia lasting for ≥ 30 seconds, while time to atrial tachyarrhythmia recurrence is determined from the Alivecor cardiac monitor. In patients not on Alivecor cardiac monitor, the first documented atrial tachyarrhythmia recurrence was made using ECG tracings during patient contact in outpatient clinic. All tracings from ECG or Alivecor monitor were reviewed by

two cardiologists, blinded to the patient's clinical subgroup classification. At the end of six months, the following clinical endpoints were measured in clinic or via telephone: Recurrence of atrial tachyarrhythmia, AF-related hospitalisations, requirement for cardioversion for AF, need for repeat ablation procedure for atrial tachyarrhythmia and need for intensification of antiarrhythmic therapy. In patients on Alivecor monitor, total AF burden (hours) was calculated. Operators and treating physicians were blinded to the AF Phenogroup status of their patients throughout the entirety of the study period. Operators and treating physicians were blinded to the AF Phenogroup status of their patients throughout the entirety of study period. In Chapter 3, with AF Phenogroup was determined by the presence or absence of a ρ gradient between the PV and LA. Patients with a positive ρ gradient between the PV and LA were classified under AF Phenogroup 1 and was associated with improved clinical outcomes after PVI-only ablation. Conversely, AF patients with a negative ρ gradient between PV and LA were classified under AF Phenogroup 2, and these patients had poorer clinical outcomes, with higher AF burden and earlier AF recurrences, when compared to AF Phenogroup 1.

Statistical analysis

Data were reported as the mean (standard deviation, SD) or the median [interquartile range, IQR] for parametric and non-parametric data, respectively. Data normality was checked using the Shapiro-Wilk test. Categorical variables were presented as n (%) and differences between groups were examined using the χ^2 test. Continuous variables were analysed using Student's t-test or Wilcoxon-rank sum test, where appropriate. Kaplan Meier curve and log-rank test were used to compare freedom from atrial tachyarrhythmia between clinical subgroups. Statistical analysis was performed using STATA 15.1 with α at $P < .05$.

Figure 7.1: Flow chart of patient analysis for chapter 7

7.4 Results

Results for Chapter 7 are divided into three sections: -

In section 1, we explore the associations between abnormal LV GLS, with the spatial distribution of renewal rate constants in the LA, LA structural and functional parameters, and RA structural and functional parameters, when compared to patients with normal LV GLS.

In section 2, we further explore the associations between the presence of abnormal LV GLS specifically in patients with normal LV ejection fraction with the spatial distribution of renewal rate constants in the LA and biatrial structural and functional parameters.

In Section 3, we analyse the influence of abnormal LV GLS on electrophysiologic characteristics and clinical outcomes in AF Phenogroup 2 patients.

Section 1: Association between renewal rate constants with baseline characteristics, LA and RA structural and functional parameters, spatial distribution of fibrillatory dynamics and clinical outcomes post ablation, in patients with abnormal LV GLS

Patient baseline characteristics

For this analysis, n=35 patients' echocardiographic and demographic data were eligible for final analysis, with n=14 patients excluded due to inability to induce AF during index procedure (n=3), hemodynamic instability during procedure (n=2), frequent AF termination (n=1), atypical atrial flutter (n=1) and incomplete echocardiographic data (n=1) and poor echocardiographic images and tracking for LV GLS analysis/interpretation (n=7). A flow chart for patient analysis for LV GLS measures is as represented in

Figure 7.1. After six months, follow-up data was available in n=34 patients with n=1 patient lost to follow-up.

With regards to patient baseline characteristics, the mean age (years) of the total cohort was 58.3 ± 9.4, 31% female, mean BMI (kg/m^2) was 31.3 ± 4.6 while the mean CHA_2DS_2-VASc score was 1.8 ± 1.5 (Table 7.1). Structurally, the measured indexed LA volume was 43.5 ± 8.9 ml/m^2, minimum 3D LA volume (ml^3) was 41.7 ± 18.9, maximum 3D LA volume (ml^3) was 70.4 ± 20.1, mean indexed RA end-systolic volume was 29.2 ± 8.1 ml/m^2 and the mean RA area was 28.3 ± 3.6 m^2 (Table 1). LA functional echocardiographic parameters were as follows: the measured LA ejection fraction (%) was 39.8 ± 13.2, LA reservoir function (%) was 18.6 ± 10, LA conduit function (%) was -11.4 ± 4.7 and LA contractile function (%) was -6.3 ± 13.6. The measured RA functional parameters were as follows: RA ejection fraction (%) was 42.3 ± 13.2, mean RA conduit function (%) was -17 ± 5.7, mean RA contractile function (%) was -9.7 ± 7.6, and the mean RA reservoir function (%) was 26.8 ± 11.1 (Table 1). Diastolic dysfunction was present in n=11(31.4%) of AF patients, while the measured mean LV E/e', a surrogate marker of LV filling pressure was 8.5 ± 4.3.

Relationship between patient demographics and echocardiographic markers of LA and RA structural and functional remodelling with LV global longitudinal strain

We analysed patients according to two groups:

1) Group 0: Normal LV GLS.

2) Group 1: Abnormal LV GLS, defined as > -17% in men and > -18% in women (More positive values of LV GLS indicate more abnormal LV longitudinal strain).

To determine cut off for normal LV GLS in our cohort, we used the reference ranges for LV GLS provided by the World Alliance Society of Echocardiography Normal Values Study, a prospective study involving

n=1882 normal subjects, with the lower limit of LV GLS observed to be -17% in men and -18% in women (695).

Patient baseline demographics: The proportion of AF patients with normal LVEF and normal LV GLS was 51.4% (n=18), normal LVEF and abnormal LV GLS was 31.4% (n=11) and abnormal LVEF and abnormal LV GLS was 17.2% (n=6) (Figure 7.2).

Patients with normal LV GLS had a lower incidence of history of CHF, a lower CHA_2DS_2-VASc score and had a diagnosis of paroxysmal AF, when compared to patients with normal LV GLS (3 (16.7%) versus 12 (70.6%), P=0.001; 1.3 ± 1.3 versus 2.4 ± 1.5, P=0.03; 12 (63.2%) versus 3 (17.6%), P=0.007, respectively) (Table 7.1).

LV structure and function: The mean LV ejection fraction was higher in patients with normal LV GLS, but no significant difference was observed in the mean LV GLS between both groups (Table 1) (64.6 ± 4.8 versus 51.8 ± 9.5, P<0.001; -19.6 ± 1.6 versus -14.2 ± 2.0, P<0.001, respectively). No significant differences were observed in the indexed LV systolic and diastolic dimensions (Table 7.1).

LV diastolic parameters: The presence of diastolic dysfunction was significantly higher in AF patients with abnormal LV GLS, when compared to those with normal LV GLS (n=9(52.9) versus n=2(11.1), P<0.001). While E/A ratio is also higher in patients with abnormal LV GLS (2.6 ± 2.6 versus 1.2 ± 0.3, P=0.03, no significant difference was observed in LV E/e', a surrogate marker of LV filling pressures (9.2 ± 4.5 versus 7.8 ± 1.7, P=0.23) (Table 7.1).

LA structure and function: The mean indexed LA volume, minimum and maximum 3D LA volume was lower in patients with normal LV GLS when compared with patients with abnormal LV GLS (38.6 ± 5.5 versus 48.7 ± 9.0, P=0.005; 32 ± 9.8 versus 53.6 ± 20.8), P=0.001; 62.7 ± 12.5 versus 79.8 ± 23.9, P=0.02, respectively) (Table 7.1). Functionally, in patient with normal LV GLS, the mean LA ejection fraction (%) and LA reservoir function (%) was significantly higher compared to patients with abnormal LV GLS (47.7 ±

8.9 versus 30.9 ± 11.5, P<0.001; 22.8 ± 11.4 versus 13.9 ± 5.3, P=0.008) but no significant differences were observed in the mean LA conduit and contractile function, comparing both groups (Table 7.1).

RA structure and function: The mean indexed RA end systolic volume is lower in AF patients with normal LV GLS (26.6 ± 7.0 versus 32.6 ± 8.8, P=0.04), but no difference was observed in the RA area in both groups (P=0.1). Functionally, the mean RA ejection fraction (%), RA reservoir function (%) and RA contractile function (%) were significantly higher in AF patients with normal LV GLS (49.5 ± 11.7 versus 34 ± 9.7, P<0.001; 32.6 ± 10.7 versus 20.1 ± 7.2, P<0.001 and -14.2 ± 6.4 versus -4.5 ± 5.3, P<0.001, respectively), with no significant differences observed in the RA conduit function (%), P=0.13 (Table 7.1).

Fibrillatory dynamic analysis using renewal approach in AF patients with abnormal LV GLS

Spatial distribution of ρ in the LA: No significant differences were observed between AF patients with normal versus abnormal LV GLS, comparing mean PV ρ and non-PV ρ, mean posterior wall ρ and non-posterior wall ρ and mean LA ρ and RA ρ (Table 7.2). When all ten individual LA locations were considered, only the mean LA anterior wall ρ was significantly higher in patients with normal LV GLS, when compared with patients with abnormal LV GLS (1.21 ± 0.11 versus 1.15 ± 0.07, P=0.05) (Table 7.3).

Spatial distribution of ρ in the RA: No significant differences were observed in the mean ρ in all six RA locations sampled, comparing AF patients with normal versus abnormal LV GLS (Table 7.4).

Findings

In our cohort of AF patients, we made the following observations: -

1) AF patients with abnormal LV GLS were more likely to be persistent AF patients with a higher CHA_2DS_2-VASc score.
2) There was evidence of biatrial structural and functional remodelling was observed in AF patients with abnormal LV GLS.

a. Specifically, indexed LA volume (ml^3/m^2) along with 3D-derived minimum (ml^3) and maximum LA volume (ml^3) were larger in patients with abnormal LV GLS. Functionally, LA ejection fraction (%) and LA reservoir function (%) were significantly lower in this cohort.
b. Interestingly, markers of RA structural and functional remodelling were also observed in patients with abnormal LV GLS, including a larger indexed RA end systolic volume (ml^3/m^2), a lower RA ejection fraction (%) and lower RA contractile function (%)

3) In AF patients with normal LV GLS, the mean LA anterior wall ρ was significantly higher compared to AF patients with abnormal LV GLS. No significant differences were observed in spatial distribution of ρ in the RA.

Discussion

Assessment of LV systolic function has been the mainstay of risk stratification, management, and prognostication of various cardiac diseases. The most used echocardiographic method for this purpose is the measurement of LV systolic function using Simpson's biplane. However, there are multiple limitations to this method, including dependency on cardiac loading conditions, interobserver variability, translational motion errors, foreshortening, heart rate and geometric assumptions (696).

To illustrate, patients with subclinical myocardial dysfunction, with normal LVEF or patients with HFpEF would not necessarily be identified using this conventional method. For instance, in n=52 AF patients with LVEF>50% who underwent catheter ablation, no significant changes were observed in the LVEF after six months follow up (60 ± 6 vs. 59 ± 9%, *P* = 0.22) (697). In another prospective study involving n=78 AF patients with preserved LVEF undergoing catheter ablation for AF, a significant improvement in LV circumferential strain was observed in AF patients who maintained sinus rhythm after one year followed up, with no significant changes observed in the measured LVEF, while deterioration in LV longitudinal strain and strain rate was observed in AF patients with arrhythmia recurrence (694).

An emerging echocardiographic method to detect cardiac systolic dysfunction is using echocardiographic strain imaging, which provides accurate quantification of the myocardial longitudinal shortening. LV GLS has been shown to identify subclinical myocardial dysfunction in various cardiac diseases, including ischemic heart disease, AF, chemotherapy-induced myocardial dysfunction, valvular heart disease and patients with heart transplant (698-701). Crucially, in these patients, it allows prognostication and clinically, it helps clinicians determine the optimal timing for interventions. In patients with chemotherapy or radiation-induced cardiac injury, LV GLS has been shown to be more sensitive for the detection of subclinical myocardial dysfunction, when compared to LV ejection fraction (702, 703). In patients with small LV cavities or concentric hypertrophy, LV GLS is a better measure of LV systolic function, compared to the conventional use of LV ejection fraction (704). Clinically, a recent meta-analysis was performed

comparing the utility of LV ejection fraction, versus LV global longitudinal strain (GLS), including sixteen studies and n=5721 adults). A significant association was observed between mortality with each standard deviation change in baseline GLS (HR 0.5, 95% CI 0.36-0.69, P<0.002) while no significant association was observed with LV ejection fraction (HR 0.81, 95% CI 0.72-O.92, P=0.57) (705).

Previous studies have suggested a significant link between AF and LV systolic dysfunction. Some studies argue that AF is a consequence of LV systolic dysfunction, while others suggest that AF could potentially be the cause of LV dysfunction in a subset of patients. LV dysfunction has previously been linked with up to six-fold risk of AF in women when compared to men (339). In patients with pre-existing LV systolic dysfunction, the presence of AF has been associated with unfavourable New York Heart Association (NYHA) functional classification (NYHA class 4), when compared to patients with milder heart failure symptoms (NYHA class 1 and 2) (706). Mechanistically, a few different pathways have been proposed 1) acute atrial stretch, in setting of increased LA pressure secondary to heart failure, stimulating stretch-activated channels leading to increase in both atrial dispersion refractoriness and anisotropy, maintaining AF (707, 708) 2) increased production of angiotensin 2 and catecholamines in heart failure predisposes to atrial fibrosis, which promotes AF (709) 3) changes in ion channels in heart failure patients, specifically, a decrease in I_{Ks} density and downregulation of Atrial I_{CaL} (710). It is also likely that AF itself is the cause for the underlying cardiomyopathy. In n=56 drug-refractory persistent AF patients with LV ejection fraction ≤ 40%, AV node ablation and pacemaker implantation was associated with improvement of LV ejection fraction in n=16(29%) of patients, suggesting the reversibility of LV systolic dysfunction in a cohort of AF patients (711). In patients with heart failure secondary to AF, some studies have suggested that a rhythm control strategy may be beneficial for these patients, when compared to rate control strategy. For instance, in n=68 persistent AF patients with idiopathic cardiomyopathy, with an LV ejection fraction ≤ 45% as determined using CMR, absolute improvement in LV ejection fraction was significantly higher in AF patients who underwent catheter ablation (18 ± 13%), when compared to AF patients who underwent

rate control strategy (4.4 ± 13%), P< 0.001 after six months follow up. In addition, in the cohort of AF patients who underwent catheter ablation, the observed improvement in LV ejection fraction was also significantly higher in patients without CMR evidence of delayed gadolinium enhancement (DGE) in the LV, when compared to patients with DGE (712). In another randomised study involving a cohort of n=363 AF patients with HFrEF (median LVEF 32.5% in ablation group versus median LVEF 31.5% in the medical therapy group), Marrouche et al showed significantly lower mortality (P=0.01), lower hospitalisations for heart failure (P=0.004) and lower death from cardiovascular causes (P=0.009) in patients who underwent catheter ablation, compared to those who were treated with medical therapy (rate or rhythm control), after a median follow up of 37.8 months (10). Similarly, a recently published large retrospective study which included n=834735 propensity-matched AF patients, showed a significantly lower risk of cardiovascular death, heart failure hospitalisations and systemic embolism/stroke in AF patients who underwent ablation, compared to non-ablation AF patients (HR 0.38, 95% CI 0.32–0.62, P<0.001; HR 0.39, 95% CI 0.33–0.46, P<0.001; HR 0.44, 95% CI 0.37–0.53, P<0.001, respectively). However, the mortality risk was non-significant in elderly patients ≥ 75 years likely due to competing risk of death from other comorbidities (713). Mechanistically, it is still unclear how AF results in cardiomyopathy, although some studies suggest the potential role of calcium mishandling in the left ventricle with AF and the loss of atrial emptying in AF resulting in activation of the sympathetic nervous system, increased LV filling pressures, and diastolic dysfunction (714-716)

Abnormal LV GLS is predictive of new-onset AF. To illustrate, a retrospective study involving n=675 participants of the Northern Manhattan Study (NOMAS) study, mean age 71±9 years followed up for 63.6 months showed that an abnormal GLS, defined as >-14.7%, measured at enrollment was an independent predictor of new-onset AF (HR 3.2, 95% 1.4-7.5, P=0.007). In this cohort, the risk of developing AF associated with an abnormal GLS was observed to be incremental to that of an abnormal indexed LA volume (717). In another prospective study involving n=531 patients who had cryptogenic stroke, but no

history of AF, Kawakami et al observed that LV GLS had comparable predictive value with LA pump and LA reservoir function for new-onset AF, with an area under the curve of 0.841, 0.825 and 0.851, respectively (718). Interestingly, this study observed that the predictive value of LA strain for new-onset AF was higher than LV GLS in patients with normal LA volume, while the predictive value of LV GLS was significantly better for new-onset AF than LA strain in patients with an enlarged LA volume (718). In another observational study involving n=373 patients with ST-segment elevation myocardial infarction, LV GLS was an independent predictor for new-onset AF (HR 1.12, 95% CI 1 – 1.25, P=0.042), adjusting for traditional cardiovascular risk factors after a median follow up of 5.5 years(719). On the contrary, another retrospective study involving n=27 male veteran endurance athletes with lone AF, mean age of 59.9 ± 7.4 years, peak LA and RA longitudinal strain was significantly lower in participants with AF, observing no significant differences in LV GLS when compared to control (720). A few hypotheses have been raised about the mechanistic links between subclinical LV dysfunction and incident AF. Firstly, a previous study has observed an association between abnormal LV GLS and reduced LA reservoir function (as LA reservoir depends on the longitudinal systolic descent of the mitral annulus) which, by itself is a significant predictor of new-onset AF (641). Secondly, abnormal LV GLS has been associated with multiple traditional cardiovascular risk factors which contribute towards AF development, including hypertension, diabetes mellitus and vascular disease (721).

The presence of subclinical LV dysfunction measured using LV GLS has been linked to adverse cardiovascular outcomes in AF patients. In n=1483 patients with newly diagnosed AF, the presence of abnormal LV GLS, defined as >-14.7% was associated with higher BNP levels, higher CRP levels, higher E/e' levels and more impaired LV ejection fraction levels (722). In addition, worst clinical outcomes including higher combined rates of heart failure admission and death were observed in patients with abnormal LV GLS, despite a normal LV ejection fraction, when compared to AF patients with both normal LV GLS and LV ejection fraction after 3 years follow up (722).

The clinical importance of identifying AF patients with subclinical LV dysfunction in view of dictating future therapies is less clearly defined. However, in AF patients with compromised cardiac function determined by LVEF, catheter ablation is associated with improved clinical outcomes. In the CASTLE-AF study which randomised n=363 AF patients with LVEF < 35% to catheter ablation versus medical therapy, a significantly lower incidence of all cardiovascular mortality and HF hospitalisations were observed in AF patients randomised to catheter ablation (10). Further, a recently published meta-analysis involving seven randomised control trials comparing catheter ablation (n=429) to medical therapy (n=427) (inclusive of both rate and rhythm control strategy) showed significant reduction in mortality (HR 0.5, 95% CI 0.34-0.74, P=0.0005), reduction in HF hospitalisations (HR 0.56, 95% CI 0.44-0.71, P<0.0001) and improvement in LVEF (mean difference 7.48, 95% CI 3.7-11.3, P<0.0001) in AF patients who underwent catheter ablation. However, no studies to date have investigated the effect of catheter ablation versus medical therapy on clinical outcomes of AF patients with abnormal cardiac function as determined by LV GLS. However, there have been studies suggesting there may be incremental clinical benefit of AF ablation in AF patients with impaired myocardial function but normal LVEF. In a case-control study involving n=86 propensity-matched HFpEF patients with AF, significantly lower arrhythmia recurrence rates, HF hospitalisations, death and HFpEF resolution were observed in patients who underwent catheter ablation, compared to medical therapy (723). Similarly, in another retrospective study comparing n=35 AF patients with HFpEF to AF patients with no HF, Rattka et al observed echocardiographic evidence of LV reverse remodelling, specifically a significant decrease in LV mass index and interventricular diastolic septal thickness associated with improvement in NYHA functional class, in AF and HFPEF patients (388). However, recurrence of AF post catheter ablation was significantly higher in the HFpEF group compared to patients without HFpEF after three years of follow-up (57% versus 79%, P=0.049) (388).

Conclusion and future directions: In RENEWAL-AF, we observed an association between adverse echocardiographic markers of LA and RA structural and functional remodelling with abnormal LV GLS. In

patients with abnormal LV GLS, there was a non-significantly higher incidence of adverse clinical outcomes post PVI-only procedure, namely a higher AF burden, need for intensification of anti-arrhythmic therapy and need for electrical cardioversion. While catheter ablation for AF has been shown to improve clinical outcomes in AF patients with LV systolic dysfunction, no studies to date have investigated clinical outcomes in AF patients with evidence of subclinical LV dysfunction measured by LV GLS. Given the findings from this study, it may be that this cohort of AF patients may also benefit from an earlier intervention from a catheter ablation procedure, which needs to be further investigated in randomised control studies.

Tables

Table 7.1: Baseline demographics and echocardiographic parameters in all patients, in patients with abnormal LV GLS and patients with normal LV GLS.

Baseline Demographics	**Mean (SD) or n [%] (N=35)**	**Normal LV GLS (N=18)**	**Abnormal LV GLS (N=17)**	**P-Value**
Age (years)	58.3 (9.4)	56.8 (10.1)	59.9 (8.6)	0.33
BMI (kg/m^2)	31.3 (4.6)	30.6 (4.7)	32.1 (4.4)	0.34
Sex, female [%]	11 [31]	6 [33.3]	5 [29.4]	0.8
Diabetes mellitus [%]	3 [9]	3 [16.7]	0 [0]	0.08
Hypertension [%]	14 [40]	5 [27.8]	9 [52.9]	0.13
Vascular disease [%]	7 [20]	4 [22.2]	3 [17.6]	0.74
Hyperlipidemia [%]	10 [28.6]	5 [27.8]	5 [29.4]	0.92
OSA [%]	13 [37]	5 [27.8]	8 [47.1]	0.24
Heart failure [%]	15 [42.9]	3 [16.7]	12 [70.6]	0.001
CVA [%]	5 [14]	1 [5.9]	4 [23.5]	0.13
Smoking history [%]	10 [28.6]	4 [22.2]	6 [35.3]	0.39
Alcohol intake [%]	22 [62.9]	11 [61.1]	11 [64.7]	0.83
CHA2DS2-VASc score	1.8 (1.5)	1.3 (1.3)	2.4 (1.5)	0.03
Paroxysmal AF [%]	15 [44]	12 [63.2]	3 [17.6]	0.007
AF Phenogroup 1 [%]	13 [37.1]	9 [50]	4 [23.5]	0.1
Presence of LA to RA gradient [%]	17 [50]	9 [50]	8 [47.1]	0.7
LV GLS [%]	-16.9 (3.3)	-19.6 (1.6)	-14.2 (2.0)	<0.001
LV ejection fraction [%]	58.4 (9.8)	64.6 (4.8)	51.8 (9.5)	<0.001
LV ESVi (ml^3/m^2)	26 (13.2)	23 (11.0)	28.9 (14.8)	0.2
LV EDVi (ml^3/m^2)	52.4 (17.1)	50.8 (17.7)	53.9 (16.8)	0.6

LA volume index (ml^3/m^2)	43.5 (8.9)	38.6 (5.5)	48.7 (9.0)	0.005
3D minimum LA volume (ml^3)	41.7 (18.9)	32 (9.8)	53.6 (20.8)	0.001
3D maximum LA volume ml^3)	70.4 (20.1)	62.7 (12.5)	79.8 (23.9)	0.02
LA ejection fraction [%]	39.8 (13.2)	47.7 (8.9)	30.9 (11.5)	<0.001
LA reservoir function [%]	18.6 (10)	22.8 (11.4)	13.9 (5.3)	0.008
LA conduit function [%]	-11.4 (4.7)	-12.5 (4.5)	-10.2 (4.7)	0.15
LA contractile function [%]	-6.3 (13.6)	-8.7 (17.9)	-3.7 (5.4)	0.29
RA ejection fraction [%]	42.3 (13.2)	49.5 (11.7)	34 (9.7)	0.0005
RA reservoir [%]	26.8 (11.1)	32.6 (10.7)	20.1 (7.2)	0.0009
RA conduit [%]	-17 (5.7)	-18.5 (6.7)	-15.4 (3.9)	0.13
RA contractile [%]	-9.7 (7.6)	-14.2 (6.4)	-4.5 (5.3)	0.0001
RA area (cm^2)	20.7 (3.7)	19.7 (3.5)	21.8 (3.8)	0.1
RA ESVi ($ml3/m^2$)	29.5 (8.4)	26.6 (7.0)	32.6 (8.8)	0.04
LV E/e’	8.5 (4.3)	7.8 (1.7)	9.2 (4.5)	0.23
E/A ratio	1.6 (1.5)	1.2 (0.3)	2.6 (2.6)	0.03
Mitral e’ septal velocity (cm/s)	11 (14.4)	14.2 (20)	7.8 (3)	0.2
Mitral e’ lateral velocity (cm/s)	10.7 (3.3)	9.8 (3)	11.6 (3.4)	0.1
Mitral E velocity (cm/s)	67.6 (24.4)	60.5 (24.7)	75.7 (22.1)	0.07
Presence of diastolic dysfunction [%]	11 [31.4]	2 [11.1]	9 [52.9]	<0.001

Abnormal LV GLS is defined as <18% in women and <17% in men. Data presented in mean (standard deviation) or n [%]. BMI, body mass index; CVA, cerebrovascular accident; LA, left atrial; RA, right atrial; LV, left ventricle; GLS, global longitudinal strain; ESVi, end systolic volume index; EDVi, end diastolic volume index.

Table 7.2: Comparison between mean ρ in different atrial locations, between AF patients with normal LV GLS and abnormal LV GLS.

LA location	Normal LV GLS (n=18)	Abnormal LV GLS (n=17)	P-value
Mean PV ρ	1.19 ± 0.13	1.19 ± 0.06	0.99
Mean non-PV ρ	1.23 ± 0.09	1.21 ± 0.06	0.62
Mean posterior wall ρ	1.22 ± 0.14	1.21 ± 0.07	0.77
Mean non-posterior wall ρ	1.23 ± 0.09	1.2 ± 0.08	0.4
Mean LA ρ	1.21 ± 0.09	1.20 ± 0.05	0.72
Mean RA ρ	1.24 ± 0.12	1.21 ± 0.13	0.5

Abnormal LV GLS is defined as <18% in women and <17% in men. Non-PV includes all sampled non-pulmonary vein locations. Non-posterior wall includes all sampled non-pulmonary vein locations without the LAA (left atrial appendage). Data presented as mean ± standard deviation.

Table 7.3: Comparison between mean ρ in different LA locations, between AF patients with normal LV GLS and abnormal LV GLS.

LA location	Normal LV GLS (n=18)	Abnormal LV GLS (n=17)	P-value
LAA ρ	1.29 ± 0.12	1.22 ± 0.18	0.22
High posterior wall ρ	1.23 ± 0.15	1.16 ± 0.15	0.19
Low posterior wall ρ	1.23 ± 0.24	1.22 ± 0.07	0.85
LA anterior ρ	1.21 ± 0.11	1.15 ± 0.07	0.05
LA septal ρ	1.18 ± 0.11	1.20 ± 0.1	0.57
LA lateral ρ	1.22 ± 0.11	1.22 ± 0.18	0.99
LIPV ρ	1.18 ± 0.22	1.16 ± 0.13	0.69
LSPV ρ	1.19 ± 0.16	1.21 ± 0.13	0.76
RSPV ρ	1.21 ± 0.15	1.21 ± 0.15	0.99
RIPV ρ	1.18 ± 0.12	1.16 ± 0.1	0.64

Abnormal LV GLS is defined as <18% in women and <17% in men. Data presented as mean ± standard deviation.

Table 7.4: Comparison between mean ρ in different RA locations, between patients with normal LV GLS compared with abnormal LV GLS

LA location	Normal LV GLS (n=18)	Abnormal LV GLS (n=17)	P-value
SVC-RA junction ρ	1.25 ± 0.4	1.19 ± 0.18	0.67
CTI ρ	1.16 ± 0.1	1.2 ± 0.11	0.32
RA posterior ρ	1.2 ± 0.1	1.2 ± 0.08	0.8
RAA ρ	1.31 ± 0.23	1.38 ± 0.44	0.57
RA septal ρ	1.21 ± 0.12	1.18 ± 0.15	0.45
RA lateral ρ	1.28 ± 0.18	1.18 ± 0.21	0.2

Abnormal LV GLS is defined as <18% in women and <17% in men. Data presented as mean ± standard deviation.

Figures

Figure 7.2: Proportion of AF patients with normal LVEF and normal LV GLS, normal LVEF but abnormal LV GLS and abnormal LVEF and abnormal LV GLS.

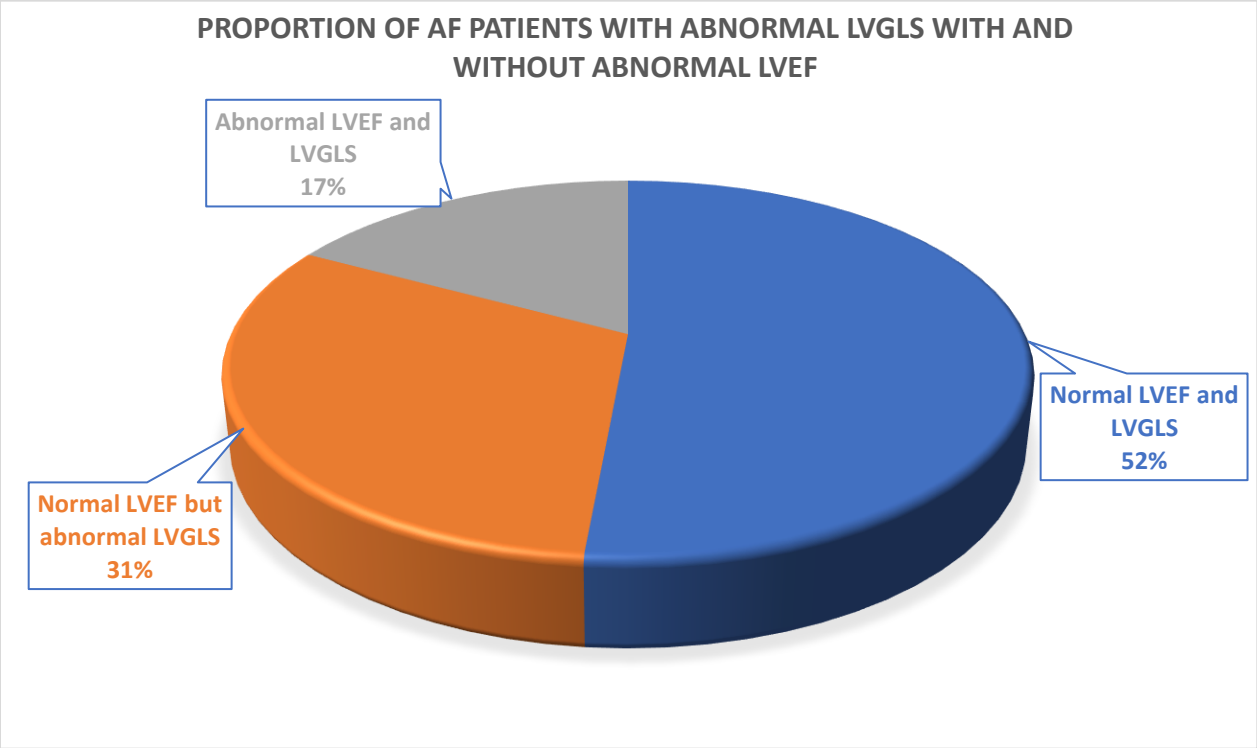


Figure 7.2 showing proportion of AF patients with abnormal LV GLS with and without an abnormal LVEF. Abnormal LV GLS is defined as <18% in women and <17% in men and abnormal LVEF is defined as LVEF<50%. Data presented in (%).

Section 2: Association between baseline demographics and echocardiographic parameters of atrial structural and functional remodelling with normal versus abnormal LV GLS in patients with normal LV EF.

Baseline demographics: In our cohort, n=18 AF patients had a normal LV EF and LV GLS and n=11 AF patients had abnormal LV GLS but normal LV EF (Table 7.6). When baseline demographics were compared, patients with normal LV EF and normal LV GLS had a lower CHA2DS2-VASc score (1.3 ± 1.3 versus 2.5 ± 1.6, P=0.04), more likely to have paroxysmal AF (n=12(66.7%) versus n=3(27.7%), P=0.04) and lower history of heart failure (n=3(16.7%) versus n=7(63.6%), P=0.04) compared to patients with normal LV EF but abnormal LV GLS (Table 7.6).

LV structure and function: The mean LV ejection fraction was higher, while the mean LV GLS was significantly lower in patients with normal LV GLS, compared with patients with abnormal LV GLS, in a cohort with normal LV EF (Table 7.6) (64.6 ± 4.8 versus 57.5 ± 4.4, P=0.005; -19.6 ± 1.6 versus -14.8 ± 1.6, P<0.0001, respectively). No significant differences were observed in the indexed LV systolic and diastolic dimensions (Table 7.6).

LV diastolic function: In patients with normal LV EF, the presence of diastolic dysfunction was significantly higher in AF patients with abnormal LV GLS, compared to patients with normal LV GLS (n=6(54.5%) versus n=2(11.1%), P=0.01). The measured LV filling pressure, using LV E/e' as a surrogate and E/A ratio were significantly higher in patients with abnormal LV GLS (11 ± 4.9 versus 7.8 ± 1.7, P=0.02 and 2.6 ± 2.6 versus 1.2 ± 0.3, P=0.03, respectively) (Table 7.6).

LA structure and function: In patients with normal LV EF, the mean indexed LA volume (ml^3/m^2) and minimum 3D LA volume (ml^3) was lower in patients with normal LV GLS when compared with patients with abnormal LV GLS (38.6 ± 5.5 versus 45.1 ± 8.4, P=0.02; 32 ± 9.8 versus 53.6 ± 20.8, P=0.03, respectively) (Table 7.6). Functionally, in patients with normal LV GLS, only the mean LA ejection fraction

(%) was significantly higher compared to patients with abnormal LV GLS (47.7 ± 8.9 versus 34.7 ± 11.1, P=0.0002), with no significant differences observed in other LA strain parameters (Table 7.6).

RA structure and function: In patients with normal LV EF, no significant differences were observed in the mean indexed RA end-systolic volume (ml^3/m^2) (P=0.32) or the RA area (P=0.5), comparing AF patients with normal versus abnormal LV GLS, respectively (Table 7.6). Functionally, the mean RA reservoir function (%) and contractile function (%) were significantly higher in patients with normal LV GLS (32.6 ± 10.7 versus 23 ± 7.5, P=0.03 and 14.2 ± 6.4 versus -6.8 ± 6.1, P=0.01, respectively), but no significant differences were observed in the RA ejection fraction (%) or the RA conduit function (%) (Table 7.6).

Fibrillatory dynamic analysis using renewal approach in AF patients with abnormal LV GLS but normal LV EF

Spatial distribution of ρ in the LA: No significant differences were observed in AF patients with normal LV EF, comparing patients with normal LV GLS versus abnormal LV GLS, with regards to mean PV ρ and non-PV ρ, mean posterior wall ρ and non-posterior wall ρ and mean LA ρ and RA ρ (Table 7.7). When all ten individual LA locations were considered, no significant differences were observed in all LA locations sampled (Table 7.8).

Spatial distribution of ρ in the RA: No significant differences were observed in the mean ρ in all six RA locations sampled in AF patients with normal LV EF, comparing patients with normal LV GLS versus abnormal LV GLS (Table 7.9).

Findings

In AF patients with normal LV EF but abnormal LV GLS, we observed the following: -

1) AF patients with abnormal LV GLS were more likely to have persistent AF, a higher CHA_2DS_2-VASc score and a previous history of congestive heart failure.
2) Echocardiographically, AF patients with abnormal LV GLS had a larger indexed LA volume and minimum 3D LA volume and a lower LA ejection fraction, with no other abnormalities seen in other LA functional parameters.
3) AF patients with abnormal LV GLS but normal LV EF were more likely to have underlying diastolic dysfunction and a higher LV filling pressure, measured echocardiographically by LV E/e'.
4) Echocardiographic markers of functional remodelling were also observed in the RA, without any overt structural RA changes.
5) No significant differences were observed in the spatial distribution of rho values between both groups in both the LA and RA, despite evidence of structural and functional remodelling seen in the atrium.

Discussion

Limited studies to date have described the association between abnormal LV GLS with structural and functional remodelling in the LA and RA in patients with normal LV EF. It is likely that a proportion of these patients with abnormal LV GLS, but normal LV EF consists of patients with HFpEF. The association between HFpEF with both incidence of AF and cardiovascular outcomes are well established (724). In patients with HFpEF, LV GLS has been shown to significantly correlate with LV end-diastolic pressures, suggesting that LV GLS could be used as an estimate of raised LV filling pressure (725). Another recent study has also shown a link between abnormal GLS and HFpEF, which is associated with AF (726, 727). In a meta-analysis involving n=2284 HFpEF patients and n=2302 controls, Morris et al observed a significantly lower higher

LV GLS (more positive indicating worse LV GLS) in patients with HFpEF, compared to controls with a mean LV GLS of -15.7% versus -19.9%, P<0.001 (726). Additionally, in patients with HFpEF, abnormal GLS was associated with worst cardiovascular outcomes including a higher risk of cardiovascular mortality and heart failure hospitalisations, when compared to HFpEF patients with normal LV GLS (HR 2.14, 95% CI 1.26 – 3.66 and HR 1.94, 95% CI 1.22 – 3.07, respectively) (726). In a prospective observational study that compared clinical outcomes between n=14 964 AF patients with HFpEF (LV ejection fraction ≥ 50%, heart failure with mildly reduced ejection fraction (HFmREF) (LV ejection fraction 40-49%) and HFrEF (LV ejection fraction <40%)), the presence of HFpEF and HFmREF were both independently associated with a higher risk of HF hospitalisations and mortality, when compared to HFrEF (682).

Another finding from this study is the observation of negative RA functional remodelling in AF patients with normal LV EF but abnormal LV GLS. The presence of RA structural and functional remodelling has also been linked to HFpEF and negative cardiovascular outcomes. In patients with HFpEF with evidence of RA structural remodelling, defined as indexed RA volume >39 mL/m^2 (men) and >33 mL/m^2 (women), a higher prevalence of AF has been observed and is associated with worst cardiovascular outcomes including all-cause mortality or heart failure hospitalisations. Mechanistically, adverse RA functional changes observed are likely a consequence of higher LV filling pressures, leading to a higher RV and subsequently RA filling pressure (728).

Limitations

1. In the absence of cardiac NT-proBNP levels and patient-specific questionnaires about symptoms of HFpEF before diagnosis, a formal diagnosis of HFpEF could not be made, in this cohort of patients with abnormal LV GLS but normal LV EF. The presence of atrial structural and functional remodelling along with the presence of echocardiographic evidence of diastolic dysfunction, seen

in the cohort of patients with abnormal LV GLS but normal LVEF, is also observed in HFpEF patients.

2. The relatively small sample size may confound results. Specifically, an interesting finding was the lack of spatial changes of fibrillatory dynamics within the LA and the RA, even with echocardiographic evidence of atrial structural and functional remodelling. These findings would need to be confirmed in a larger cohort of patients.

Conclusion

In a cohort of AF patients with normal LV EF but abnormal LV GLS, evidence of both biatrial structural and functional remodelling was observed, with no significant spatial variations in the fibrillatory dynamics in both atria. It is plausible that a certain threshold of atrial remodelling must be met, before significant spatial alterations in atrial fibrillatory dynamics, measured by rho values.

Table 7.5: Baseline demographics and echocardiographic parameters in AF patients, analysed by normal LV EF and normal LV GLS or normal LV EF but abnormal LV GLS.

Baseline demographics and echocardiographic parameters	Normal LV GLS and normal LV EF (n=18)	Abnormal LV GLS and normal LV EF (n=11)	P-Value
Age (years)	56.8 (10.1)	61.7 (9.1)	0.19
BMI (kg/m^2)	30.6 (4.7)	31.1 (3)	0.74
Sex, female [%]	6 [33.3]	5 [36.4]	0.87
Diabetes mellitus [%]	3 [16.7]	0 [0]	0.15
Hypertension [%]	5 [27.8]	5 [45.5]	0.33
Vascular disease [%]	4 [22.2]	3 [27.3]	0.76
Hyperlipidemia [%]	5 [27.8]	5 [45.5]	0.33
OSA [%]	5 [27.8]	4 [36.4]	0.63
Heart failure [%]	3 [16.7]	7 [63.6]	0.01
CVA [%]	1 [5.6]	3 [27.3]	0.1
Smoking history [%]	4 [22.2]	3 [27.3]	0.76
Alcohol intake [%]	11 [61.1]	7 [63.6]	0.89
CHA2DS2-VASc score	1.3 (1.3)	2.5 (1.6)	0.04
Paroxysmal AF [%]	12 [66.7]	3 [27.7]	0.04
Presence of LA to RA gradient [%]	8 [44.4]	6 [54.5]	0.7
AF Phenogroup 1 [%]	9 [50]	3 [27.2]	0.23
LV GLS [%]	-19.6 (1.6)	-14.8 (1.6)	<0.0001
LV ejection fraction [%]	64.6 (4.8)	57.5 (4.4)	0.0005
LV ESVi (ml^3/m^2)	23 (11)	23.3 (8.3)	0.96
LV EDVi (ml^3/m^2)	50.8 (17.7)	52.6 (17)	0.79
LA volume index (ml^3/m^2)	38.6 (5.5)	45.1 (8.4)	0.02
3D minimum LA volume (ml^3)	32 (9.8)	45.1 (17.4)	0.03
3D maximum LA volume ml^3)	64.9 (10.7)	73.1 (22.1)	0.15
LA ejection fraction [%]	47.7 (9)	34.7 (11.1)	0.0002

LA reservoir function [%]	22.8 (11.4)	15.6 (5.5)	0.07
LA conduit function [%]	-12.5 (4.5)	-10.5 (5.1)	0.29
LA contractile function [%]	-8.7 (17.9)	-5.2 (5.8)	0.56
RA ejection fraction [%]	49.5 (11.7)	40.8 (5.9)	0.06
RA reservoir [%]	32.6 (10.7)	23 (7.5)	0.03
RA conduit [%]	-18.5 (6.7)	-16 (4)	0.34
RA contractile [%]	14.2 (6.4)	-6.8 (6.1)	0.01
RA area (m^2)	19.7 (3.5)	20.8 (4.3)	0.5
Indexed RA end systolic volume (ml^3/m^2)	26.6 (7)	29.6 (8.3)	0.32
Presence of diastolic dysfunction [%]	2 (11.1)	6 (54.5)	0.01
LV E/e’	7.8 (1.7)	11 (4.9)	0.02
Mitral e’ septal velocity (cm/s)	14.2 (20)	7.2 (3)	0.26
Mitral e’ lateral velocity (cm/s)	9.8 (3)	10.2 (3)	0.76
E/A ratio	1.2 (0.3)	2.6 (2.6)	0.03
Mitral E velocity (cm/s)	60.5 (24.7)	78.5 (26)	0.08

Abnormal LV GLS is defined as <18% in women and <17% in men. Data presented as mean [SD] or n (%).

Table 7.6: Comparison between mean ρ in different atrial locations, in all patients and between AF patients with normal LV GLS and normal LV EF and normal LV EF but abnormal LV GLS.

LA location	Normal LV EF and LV GLS (n=18)	Normal LV EF and abnormal LV GLS (n=11)	P-value
Mean PV ρ	1.19 ± 0.13	1.18 ± 0.06	0.93
Mean non-PV ρ	1.23 ± 0.09	1.21 ± 0.05	0.54
Mean posterior wall ρ	1.22 ± 0.1	1.22 ± 0.08	0.93
Mean non-posterior wall ρ	1.23 ± 0.09	1.21 ± 0.07	0.53
Mean LA ρ	1.21 ± 0.09	1.20 ± 0.05	0.71
Mean RA ρ	1.24 ± 0.1	1.23 ± 0.13	0.93

Abnormal LV GLS is defined as <18% in women and <17% in men. Non-PV includes all sampled non-pulmonary vein locations. Non-posterior wall includes all sampled non-pulmonary vein locations without the LAA (left atrial appendage). Data presented as mean ± standard deviation.

Table 7.7: Comparison between mean ρ in all sampled left atrial locations in AF patients with normal LV EF, between patients with normal LV EF and normal LV GLS and in patients with normal LV EF but abnormal LV GLS.

LA locations	Normal LV EF and LV GLS (n=18)	Normal LV EF but abnormal LV GLS (n=11)	P-value
LAA	1.29 ± 0.12	1.23 ± 0.2	0.36
LA septum	1.18 ± 0.11	1.22 ± 0.09	0.35
LA anterior	1.22 ± 0.11	1.16 ± 0.07	0.16
LA high posterior	1.23 ± 0.15	1.15 ± 0.19	0.22
LA low posterior	1.23 ± 0.24	1.24 ± 0.08	0.92
LA lateral	1.22 ± 0.19	1.21 ± 0.19	0.87
LSPV	1.20 ± 0.16	1.19 ± 0.14	0.96
LIPV	1.18 ± 0.22	1.16 ± 0.15	0.8
RSPV	1.18 ± 0.12	1.17 ± 0.1	0.82
RIPV	1.21 ± 0.15	1.21 ± 0.19	0.92

Abnormal LV GLS is defined as <18% in women and <17% in men. Data presented as mean ± standard deviation.

Table 7.8: Comparison between mean ρ in different RA locations in AF patients with normal LV EF, compared patients with normal LV GLS versus patients with abnormal LV GLS.

LA location	Normal LV GLS (n=18)	Abnormal LV GLS (n=11)	P-value
SVC-RA junction ρ	1.25 ± 0.4	1.13 ± 0.1	0.45
CTI ρ	1.16 ± 0.1	1.2 ± 0.13	0.35
RA posterior ρ	1.2 ± 0.1	1.21 ± 0.1	0.95
RAA ρ	1.31 ± 0.23	1.44 ± 0.48	0.36
RA septal ρ	1.21 ± 0.12	1.19 ± 0.14	0.67
RA lateral ρ	1.28 ± 0.18	1.19 ± 0.22	0.29

Abnormal LV GLS is defined as <18% in women and <17% in men. Data presented as mean ± standard deviation.

Section 3: Influence of abnormal LV GLS on electrophysiologic characteristics and clinical outcomes in AF Phenogroup 2 patients

Rationale for section 3:

In Chapter 4, we characterised patients into AF Phenogroups, depending on location with the highest rho value (highest average PS formed per unit time). We further defined AF Phenogroup 2 patients as patients with the highest rho value in the LA body. This was associated with echocardiographic markers of LA structural remodelling and a poorer clinical outcome after the PVI-only procedure. Mechanistically, we hypothesise that this could represent a high turnover of PS or clustering of PS within the LA body.

An important observation made in Section 1 of Chapter 7 was that clinical outcomes trended non-significantly poorer in patients with abnormal LV GLS, including a non-significantly higher burden of AF, higher requirement for DCCV and higher requirement for intensification of antiarrhythmic therapy six months post PVI-only procedure. In this substudy, we hypothesise that the presence of abnormal LV GLS in AF Phenogroup 2 patients will be associated with significant adverse atrial structural and functional remodelling, with worst clinical outcomes after a PVI-only procedure, when compared to AF Phenogroup 2 patients with normal LV GLS.

Results

Baseline demographics: Out of the n=22 AF Phenogroup 2 patients, n=9 (40.9%) had normal LV GLS and n=13 (59.1%) of patients had abnormal LV GLS. Demographically, patients with abnormal LV GLS had a higher incidence of a congestive heart failure (n=9(69.2%) versus n=1(11.1%), P=0.007) and a lower prevalence of paroxysmal AF (n=3(23.1%) versus n=6(66.7%), P=0.05) (Table 8.1).

LV structure and function*:* No significant differences were observed in the indexed LV ESV (ml^3/m^2) (P=0.9) and indexed LV EDV (ml^3/m^2) (P=0.47) between groups (Table 8.1). However, LV GLS (%) and LV ejection

fraction (%) were significantly lower in AF Phenogroup 2 patients with abnormal LV GLS, compared to patients with normal LV GLS (-14.6 (1.8) versus -18.8 (1.1), P<0.001 and 52.1 (9.0) versus 63.2 (4.7), P<0.001, respectively) (Table 8.1).

LA structure and function: Structurally, minimum 3D-derived LA volume (ml^3) and LA volume index (ml^3/m^2) were significantly higher in AF Phenogroup 2 patients with abnormal LV GLS, compared with patients with normal LV GLS (58.2 (21.7) versus 33 (9.9), P=0.005 and 50.9 (7.7) versus 39.6 (6.3), P=0.002, respectively) (Table 8.1).

Functionally, LA ejection fraction (%), LA reservoir function (%) and LA contractile function (%) were all significantly lower in patients with abnormal LV GLS (29.1 (10.3) versus 47.1 (6.1), P<0.001, 12 (3.2) versus 25.3 (3.4), P<0.001 and -1.8 (3.3) versus -13 (1.8), P<0.001, respectively) (Table 8.1).

RA structure and function: Structurally, indexed RA ESV (ml^3/m^2) was significantly larger in AF Phenogroup 2 patients with abnormal LV GLS, compared to patients with normal LV GLS (32.5 (9.0) versus 24.5 (4.0), P=0.02) (Table 8.1).

Functionally, both RA ejection fraction (%) and RA reservoir (%) were also significantly lower in AF Phenogroup 2 patients with abnormal LV GLS (31.9 (3) versus 45 (4.1), P=0.012 and 18.8 (6.8) versus 45 (4.1), P=0.02, respectively) (Table 8.1).

Clinical outcomes of AF Phenogroup 2 patients, comparing patients with normal LV GLS and abnormal LV GLS.

When both groups were compared, no significant differences were observed in terms of AF recurrences (n=5 [55.6] versus n=10 [76.9], P=0.48) (Table 8.5). However, AF burden, measured in hours, trended non-significantly higher in AF Phenogroup 2 patients with abnormal LV GLS (median hours of 18 (0, 36) versus 222 (38, 324), P=0.068) (Table 8.5). No significant differences were observed concerning the need for re-

do ablation (P=0.85), the need for intensification of antiarrhythmic therapy (P=0.2), the need for AF-related hospitalisations (P=0.92) and the need for electrical cardioversion (P=0.14) comparing both groups (Table 8.5). Survival analysis revealed no significant differences in time to AF recurrence comparing AF Phenogroup 2 patients with normal versus abnormal LV GLS (HR 1.6, 95% CI, P=0.4) (Figure 7.4).

Findings

In AF Phenogroup 2 patients with abnormal LV GLS, we observed the following findings:

1. There was echocardiographic evidence of greater LA structural remodelling, as measured by indexed LA volume and minimum 3D derived LA volume and functional remodelling, as measured by LA ejection fraction, LA reservoir, and LA contraction when compared to AF Phenogroup 2 patients with normal LV GLS
2. There was echocardiographic evidence of greater structural and functional remodelling in the RA, as measured by indexed RA volume, RA ejection fraction and RA reservoir function, when compared to AF Phenogroup 2 patients with normal LV GLS.
3. There was a non-significant trend towards higher AF burden, as estimated by Alivecor cardiac monitor in AF Phenogroup 2 patients with abnormal LV GLS when compared to AF Phenogroup 2 patients with normal LV GLS.

Discussion

In chapter 4, we reported a link between AF Phenogroup 2 with a higher rate of recurrence of AF and a higher burden of AF, measured by Alivecor monitor six months post catheter ablation. In chapter 7, we observed the presence of abnormal LV GLS, a marker of poor cardiovascular outcomes in a subset of AF Phenogroup 2 patients. This was associated with greater echocardiographic evidence of atrial structural and functional remodelling, and differences in locations of atrial PS clustering with a non-significant trend towards higher AF burden, measured by AliveCor cardiac monitor six months post AF ablation.

Close associations between LV mechanics and LA structure and function have been described. Abnormalities in different LA mechanical phases have been previously linked to abnormalities in both LV systolic function and a high LV end-diastolic pressure. For instance, studies have shown the association between LA reservoir function with LV systolic dysfunction and LA contractile function with higher LV end-diastolic pressure. However, the cause/effect of AF, abnormal LV GLS and LA structural and functional remodelling is unclear. It is plausible that a subset of AF Phenogroup 2 patients likely has underlying advanced atrial remodelling, leading to both a higher AF burden and abnormal LV GLS. Another likely scenario is the presence of a higher AF burden in a cohort of AF Phenogroup 2 patients, leading to abnormal LV GLS, and consequently, abnormal LA structure and function (tachycardia-mediated cardiomyopathy). Not surprisingly, there was a non-significant trend towards worst cardiovascular outcomes post-ablation in AF Phenogroup 2 patients with abnormal LV GLS. This may be inherently linked to the presence of abnormal LV GLS itself, or the abnormal LV function, a consequence of the abnormal LV GLS.

Conclusion

In AF Phenogroup 2 patients, the presence of abnormal LV GLS was associated with a higher degree of biatrial structural and functional remodelling, and a non-significant trend towards higher AF burden, after a PVI-only ablation procedure.

Table 7.9.1 Baseline demographics and echocardiographic parameters in patients in AF Phenogroup 2, analysed by the presence or absence of an abnormal LV GLS.

Baseline Demographics	Group 0 (Normal LV GLS) (n=9)	Group 1 (Abnormal LV GLS) (n=13)	P-Value
Age (years)	59.4 (9.4)	60.5 (8.2)	0.77
BMI (kg/m^2)	30.3 (4.0)	32.1 (4.9)	0.39
Sex, female [%]	2 [22.2]	5 [38.5]	0.42
Diabetes mellitus [%]	2 [22.2]	0 [0]	0.08
Hypertension [%]	4 [44.4]	6 [46.2]	0.94
Vascular disease [%]	2 [22.2]	1 [7.7]	0.33
Hyperlipidemia [%]	2 [22.2]	3 [23.1]	0.96
OSA [%]	2 [22.2]	6 [46.2]	0.25
Heart failure [%]	1 [11.1]	9 [69.2]	0.007
CVA [%]	1 [11.1]	4 [30.8]	0.28
Smoking history [%]	3 [33.3]	4 [30.8]	0.9
Alcohol intake [%]	6 [66.7]	8 [61.5]	0.81
CHA2DS2-VASc score	1.8 (1.6)	2.5 (1.6)	0.27
Paroxysmal AF [%]	6 [66.7]	3 [23.1]	0.05
Presence of LA to RA gradient [%]	3 [33.3]	5 [38.5]	0.81
LV GLS [%]	-18.8 (1.1)	-14.6 (1.8)	<0.001
LV ejection fraction [%]	63.2 (4.7)	52.1 (9.0)	<0.001
LV ESVi (ml^3/m^2)	26.7 (13.6)	26 (10.5)	0.9
LV EDVi (ml^3/m^2)	48.1 (20.2)	54.4 (19.3)	0.47
LA volume index (ml^3/m^2)	39.6 (6.3)	50.9 (7.7)	0.002
3D minimum LA volume (ml^3)	33 (9.9)	58.2 (21.7)	0.005
3D maximum LA volume ml^3)	64.9 (10.7)	83.2 (25.7)	0.06
LA ejection fraction [%]	47.1 (6.1)	29.1 (10.3)	0.0002
LA reservoir function [%]	25.3 (3.4)	12 (3.2)	<0.001
LA conduit function [%]	-12.2 (3.5)	-10.5 (4.5)	0.35
LA contractile function [%]	-13 (1.8)	-1.8 (3.3)	<0.001
RA ejection fraction [%]	45 (4.1)	31.9 (3)	0.02
RA reservoir [%]	30.4 (10.9)	18.8 (6.8)	0.012
RA conduit [%]	-17.7 (6.9)	-15 (4.2)	0.32
RA contractile [%]	-12.9 (5.3)	-3.7 (5.5)	0.0018
RA area (cm^2)	19.1 (3.2)	21.4 (3.9)	0.18
RA ESVi (ml^3/m^2)	24.5 (4.0)	32.5 (9.0)	0.02

Abnormal LV GLS is defined as <18% in women and <17% in men. Data presented in mean (standard deviation) or n [%]. BMI, body mass index; CVA, cerebrovascular accident; LA, left atrial; RA, right atrial; LV, left ventricle; GLS, global longitudinal strain; ESVi, end-systolic volume index; EDVi, end-diastolic volume index.

Table 7.9.2: Association between abnormal LV GLS and clinical outcomes post-PVI only procedure in AF Phenogroup 2 patients.

Clinical outcomes measured	**Normal LV GLS (n=9)**	**Abnormal LV GLS (n=13)**	**P-value**
Atrial tachyarrhythmia recurrence, n [%]	5 [55.6]	10 [76.9]	0.48
Atrial tachyarrhythmia burden on Alivecor (hours)	18 (0,36)	222 (38, 324)	0.068
Escalation in antiarrhythmic therapy	1 [11.1]	5 [38.4]	0.2
Electrical cardioversion	0 [0]	3 [23.1]	0.14
Atrial fibrillation, atrial flutter and/or atrial tachycardia ablation	1 [11.1]	2 [15.4]	0.85
AF-related hospitalisations	2 [22.2]	3 [23.1]	0.92

Clinical outcome measures include atrial tachyarrhythmia recurrence, intensification of antiarrhythmic medication during follow up period, need for electrical cardioversion for AF, AF-related hospitalisations

and need for re-do AF ablation procedures. Abnormal LV GLS is defined as <18% in women and <17% in men. Data presented as mean ± standard deviation or n (%).

Figure 7.4: Survival curve analysis comparing patients with normal versus abnormal LV GLS, in AF Phenogroup 2 patients.

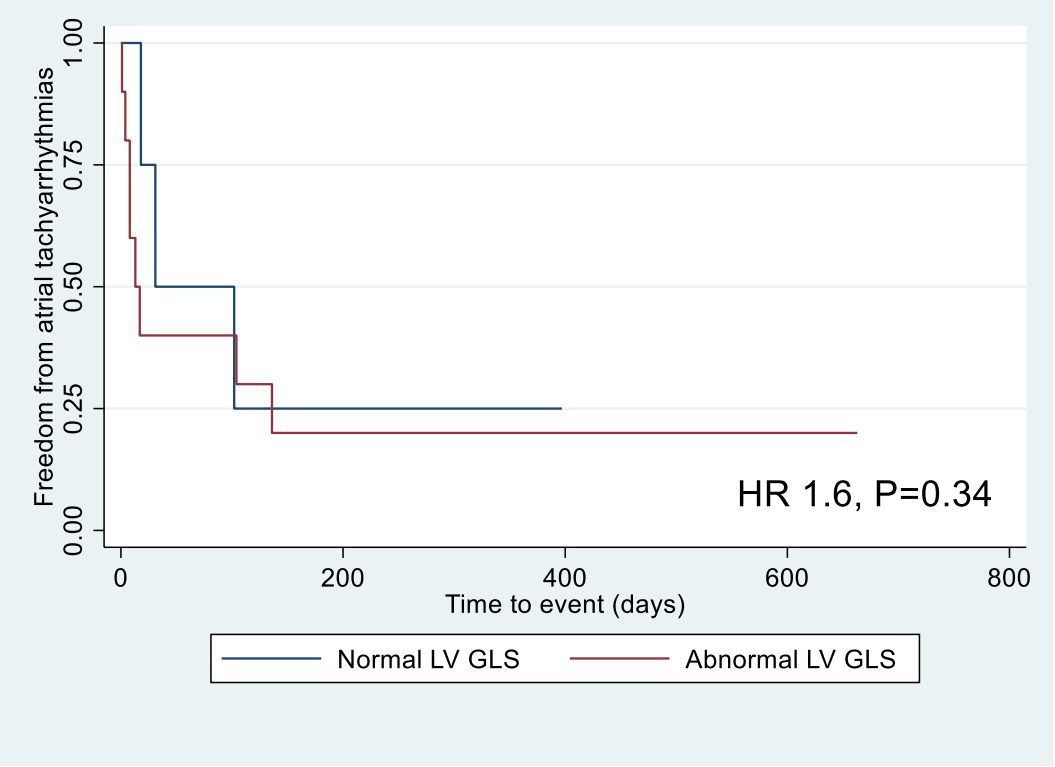


Figure 7.4: Kaplan Meier curves showing survival free time from atrial tachyarrhythmias (days) in AF Phenogroup 1 and 2 patients, comparing patients with normal LV GLS and patients with abnormal LV GLS in both groups. No significant differences in time to AF recurrence comparing AF Phenogroup 2 patients with normal versus abnormal LV GLS (HR 1.6, 95% CI, P=0.4)

Chapter 8

Relationship between renewal theory-based assessment of fibrillatory dynamics with dominant frequency analysis

8.1 Abstract

Background: As a potentially objective metric for quantitative assessment of fibrillatory dynamics, dominant frequency analysis (DF) has been previously evaluated as a tool to identify AF "drivers" and substrates. However, limited studies performed to date suggest no incremental clinical benefit from employing DF to clinically guide catheter ablation of AF. We recently showed a physiological assessment of fibrillatory dynamics could be performed using renewal theory, which determines rates of phase singularity formation (λ_f) and destruction (λ_d). Using the renewal approach, we aimed to understand the mechanistic relationship between renewal theory-based fibrillatory dynamic analysis with the spatial distribution of DF.

Methods: RENEWAL-AF is a prospective multicenter observational study recruiting AF ablation patients (ACTRN 12619001172190). We studied unipolar electrograms obtained from sixteen biatrial locations prior to ablation using a 16-electrode Advisor^{TM} HD-Grid catheter. Renewal rate constants λ_f and λ_d were calculated, and the relationships between these rate constants in regions of inter-atrial connectivity were examined. DF values were calculated in all corresponding atrial regions. To compare AF Phenogroup classification with DF, we further classified patients according to the highest DF in the pulmonary veins versus patients with the highest DF in the LA body.

Results: No significant correlations were observed between renewal rate constants (λ_f, λ_d and ρ) with DF in all ten LA locations. In all patients, the highest DF was observed in the inferior pulmonary veins, while

the highest ρ value was observed in the low posterior LA wall. When analysed by AF Phenogroup, both DF and renewal rate constants were the highest in the left inferior pulmonary veins in AF Phenogroup 1. However, no significant correlations were observed between DF PV-non PV classification and AF Phenogroup (P=0.78).

Conclusions: While some similarities were observed between the spatial distribution of DF and renewal rate constants in AF Phenogroup 1, no significant correlations were observed in all patients and AF Phenogroup 2 patients. The lack of association between DF and renewal rate constants in this cohort may be due to the known limitations of DF analysis in clinical AF recordings.

8.2 Introduction

Clinical outcomes in AF patients undergoing catheter ablation for AF remain suboptimal. Specifically, in AF patients who have AF recurrence post-PVI, ablation strategies beyond PVI remain poorly defined. Some studies have postulated that using computational and mathematical approaches, clinically significant atrial regions, and atrial regions outside of PV may be identified and targeted for ablation. However, a major challenge in developing a robust mathematical approach for fibrillatory dynamic analysis lies in the complex, chaotic and aperiodic nature of AF wavefront propagation.

Multiple studies have utilised dominant frequency (DF) analysis as a quantitative metric for fibrillatory dynamics assessment (729-731). DF analysis represents an approach to attempt measurement of local activation rate of a specific atrial region. Earlier studies have suggested atrial regions with high dominant frequency act as "driver" for AF(191). However, the real-world clinical benefit from employing these metrics to guide catheter ablation strategies in AF have been limited (439). In RENEWAL-AF, the presence of a higher PS cluster (higher average PS formation) in the pulmonary veins was associated with improved clinical outcomes from a PVI-only procedure. In chapter 8, we aim to explore the relationship between fibrillatory dynamic analysis using the renewal approach with DF analysis.

8.3 Methods

Electrophysiology study

Baseline demographics were obtained pre-procedurally and documented in an electronic clinical record form (Redcap, Vanderbilt University, VA). Electrophysiologic studies were performed five half-lives free of antiarrhythmic drug therapy, except for patients taking amiodarone. Patients were mapped under spontaneous or induced AF using the Ensite Precision electroanatomic mapping system (Abbott Cardiovascular, Plymouth MN). Advisor^{TM} HD-grid mapping catheter was used (Abbott Cardiovascular, Plymouth MN). This catheter has 16 electrodes in a square grid (13x13mm^2 grid, 3mm inter-spacing).

Unipolar electrograms were recorded at 1000 Hz (band-pass filter 0.5-500Hz). Electrograms and ECG tracings were recorded for one minute prior to ablation in ten LA locations: 1) LSPV 2) LIPV 3) RSPV 4) RIPV 5) LA high posterior wall 6) LA low posterior wall 7) Left lateral region 8) LAA 9) LA anterior region and 10) LA septum.

Signal processing

Unipolar electrogram signals were processed as described (16, 457, 472). QRS subtraction was performed, and Butterworth filters applied (16, 457, 472). Sinusoidal recomposition was applied with the dominant frequency set as wavelet period and phase computed using the Hilbert transform to construct phase maps (16, 82, 457, 472). In each phase map, PS were detected and tracked as previously described using a convolution kernel method based on topological charge (16, 457, 472). PS tracking enabled calculation of PS lifetimes and inter-formation times (times between consecutive PS formations), which also enabled construction of PS lifetime and inter-formation time distributions (16, 457, 472). PS distributions were fitted using maximum likelihood fitting to estimate the rate of PS formation (denoted as λ_f) and PS destruction (λ_d) (Figure 2) (16, 457, 472).

Dominant frequency analysis

Spectral analysis of the electrograms was performed on each of the recordings from individual atrial locations. To obtain the electrogram power spectrum, Fast Fourier transform with a spectral resolution of 0.24 Hz was performed at each atrial location. Regularity index (RI) was used to ensure reliability of DF analysis, which is defined as the ratio of power at DF and their associated frequencies (0.75 Hz) to the power of 3 to 15 Hz (191). Only points with RI above 0.2 were selected for analysis to avoid false DF detection, from poor signal-to-noise ratio.

Statistical analysis

Data were reported as the mean (standard deviation, SD) or the median [interquartile range, IQR] for parametric and non-parametric data. Data normality was checked using the Shapiro-Wilk test. Categorical variables were presented as n (%) and differences between groups were examined using the χ^2 test. Two group comparisons were analysed using Student's t-test. For each sampled LA region, the associations between DF and λ_f, λ_d and ρ values from different LA regions were evaluated using Pearson's correlation coefficient. Examples of sampled atrial regions using dominant frequency analysis, as compared to renewal approach are presented in Figure 8.3 to 8.5. Statistical analysis was performed using STATA 15.1 with α at $P < .05$.

8.4 Results

Dominant frequency analysis

In all patients, the highest DF was observed in the RIPV followed by the LIPV with a mean of 6.28 ± 1.24 and 6.25 ± 1.11 respectively, while the lowest DF was observed in the lateral LA wall with a mean of 5.65 ± 1.07 (Figure 8.1). Using the renewal theory, the highest ρ values were observed in the LAA followed by the RIPV, while the lowest ρ value was observed in the LIPV (Figure 8.2). No significant correlations were observed in all ten LA regions sampled between DF and λ_f, λ_d and ρ values.

When classified according to the atrial region with the highest DF (PV versus non-PV sites), n=18 patients (47.4%) had the highest DF in the PV while n=20 patients (52.6%) had the highest DF in non-PV sites. No correlation was observed between AF Phenogroup and DF PV-Non PV classification (P=0.78).

When analysed by AF Phenogroups:

AF Phenogroup 1: Highest DF values were observed in the LIPV and RIPV respectively, while the lowest DF value was observed in the low posterior LA wall. When compared to renewal rate constants, ρ, highest ρ values were also observed in the LIPV and the LSPV, while the lowest ρ value was observed in the anterior LA wall (Figure 8.2).

AF Phenogroup 2: Highest DF values were observed in the RIPV and low posterior LA wall, while the lowest DF value was observed in the lateral LA wall. When compared to renewal rate constant, ρ, highest ρ value was observed in the LAA and the lowest ρ value was observed in the LA septum (Figure 8.2).

Location of highest in PV comparing renewal theory and DF: Examples of three clinical cases

Patient 1 (Figure 8.3) was 51-year-old male with BMI of 37 and CHA_2DS_2-VASC of 5. The patient had persAF diagnosed 7 years prior to PVI and was on amiodarone for rhythm control**.** Echocardiographic findings included LVEF of 44 % and LAVi 62 ml/m^2.

Renewal theory-based analysis: Highest λ_f/λ_d value in the LA lateral wall (AF Phenogroup 2).

Dominant frequency analysis: Highest DF value in the LA anterior wall.

Patient 2 (Figure 8.4) was 35-year-old male with BMI of 35 and CHA_2DS_2-VASC of 0. The patient had been in persAF for 28 months prior to PVI, with one previous cardioversion and was on flecainide for rhythm control. Echocardiographic findings included LVEF of 64% and LAVi 34 ml/m^2.

Renewal theory-based analysis: Highest λ_f/λ_d values in the LSPV (AF Phenogroup 1).

Dominant frequency analysis: Highest DF value in the LA septum

Patient 3 (Figure 8.5) was 61-year-old male with BMI of 30 and CHA_2DS_2-VASC of 1. The patient has had pAF for seven years prior to PVI and was on flecainide for rhythm control. The patient was referred for PVI due to increasing frequency of symptomatic paroxysmal episodes of AF. Echocardiographic findings included LVEF of 44% and LAVi 35 ml/m^2.

Renewal theory-based analysis: Highest λ_f/λ_d values in the RSPV (AF Phenogroup 1).

Dominant frequency analysis: Highest DF value in the LA septum.

8.5 Findings and discussion

Findings

1. In AF Phenogroup 1, we observed high DF and renewal rate constants in the left inferior pulmonary veins.
2. However, regional differences in the highest DF and renewal rate constants were observed in AF Phenogroup 2 patients.
3. No significant correlations were observed between measures of renewal rate constants (λ_f, λ_d and ρ) with DF in all LA locations sampled and in the clinical case examples presented.

Discussion

Theoretically, the highest recorded DF site, which represents the highest activation rate from a local source in the atrium should correspond to a high rho value in the same region, which represents the atrial region with the highest rate of regeneration of PS. However, in our study, we observed some similarities only in AF Phenogroup 1 (both DF and renewal rate constants were high in the left inferior pulmonary veins), but not in AF Phenogroup 2 patients. In addition, no linear correlations were observed between measures of renewal rate constants and DF in all atrial sites sampled. There are a few potential reasons for this:

1) Lack of spatiotemporal stability of high DF regions in persistent AF patients

a. Using in silico computational models of AF derived from 3D-CT data from n=10 persAF patients, Li et al observed that DF spatial stability was only present in 10% of atrial sites, and temporally unstable, particularly in the regions of the PV, LAA and peri-mitral areas. Interestingly, despite the presence of spatiotemporal instability of high DF sites, virtual ablation to these atrial regions resulted in significant termination of AF or conversion to

AT in the majority of cases. However, this could simply be the consequence of ablation altering electrical wave front propagation/dynamics (732).

b. In human AF, spatiotemporal instability of high DF sites has also been observed, particularly in persistent AF patients. An earlier observational study by Sanders et al involving n=32 AF patients undergoing ablation localized high DF regions to the PV in pAF patients, and to the LA body in persAF patients (191). In addition, ablation at high DF sites in PAF patients resulted in termination and non-inducibility of AF post-ablation (191). Although Sanders et al reported that high DF regions were spatiotemporally stable, a limitation to this observation was the sequential point-by-point method used during mapping. Clinically, a study randomizing n=232 AF patients to DF-guided ablation only versus PVI in pAf patients or PVI plus DF versus PVI-only in persAF patients failed to show any incremental benefit (439). A potential reason behind this is the lack of spatiotemporal stability of high DF regions. In n=8 persAF patients, using non-contact endocardial mapping, Salinet et al observed both the presence of spatial and temporal instability in DF behaviour in the LA (733). Using a 0.25 Hz and 0.5 Hz DF threshold as a measure of temporal stability, 60% and 40% of high DF sites lost stability in the first two seconds of measurement. Interestingly, an exponential decay was observed, when the percentage of stable DF sites was plotted against time, which potentially suggests the presence of a renewal process. When spatial stability of the high DF regions was assessed, three different characteristics were observed; a) local activity, where propagation of DF is < 5% of total LA surface area b) cyclical activity, where high DF sites propagate to > 5% of total LA surface area, but returns to regions of previously high DF sites and 3) chaotic activity, where high DF sites propagate to > 5% of total LA surface area in a random fashion. Non-contact mapping over a one-minute duration showed that cyclical activity was the

predominant DF behaviour (present in all but one patient), followed by cyclical and chaotic behaviour (733). Interestingly, all three patterns of DF behaviour can also be observed in one patient if recordings were obtained over a longer duration. Similar observations of spatiotemporal instability of high DF sites have also been made on epicardial recordings on AF patients, spatially unstable even in pAf patients (730) and using multielectrode contact mapping recordings for five minutes in n=18 AF patients undergoing ablation (734).

2) **High DF sites may represent sites of collision between two opposing wavefronts (438).**

   a. Interestingly, in our study, we observed similarities between high DF site and high rho values in AF Phenogroup 1 patients, in the PV but not AF Phenogroup 2. In Chapter 5, we have shown a link between adverse LA structural and functional remodelling in AF Phenogroup 2 patients. We hypothesise that due to the presence of significant electrical and structural (fibrotic depositions) changes in AF Phenogroup 2, multiple wave front collisions due to complex architectural and ionic changes in the LA body would create erroneous high DF sites, that do not necessarily translate to regions with high atrial activation rates. This may explain the lack of clinical benefit observed in DF ablation in persistent AF patients.

   b. Conversely, in AF Phenogroup 1, where atrial structural and functional remodelling is minimal, high DF sites colocalize with high rho values to the inferior pulmonary veins, which may represent significant atrial regions contributing to AF. However, this observation could also represent wave front collisions with LA-PV junction, where architectural complexity would be relatively higher than the rest of the LA body leading to a high DF, and high rho values, in a setting of wave front collision with functional and anatomical boundaries in the LA-PV junction, leading to a high rate of regeneration of PS.

In addition, electrogram characteristics, specifically low amplitude, rounded complex fractionated electrograms (735) and intrinsic behaviour of rotors, including its tendency to meander, may lead to a lack of detection and further, spatial instability of high DF sites, as discussed above (438).

8.6 Conclusion

In this study, there was a lack of correlation between renewal rate constants with dominant frequency analysis, particularly in AF Phenogroup 2 patients. Although hypothetically, atrial regions with high DF and renewal rate constants may both represent a specific atrial region with high activation rates, the observed differences may be due to known limitations in DF analysis, which hampers its widespread use in clinical practice.

8.7 Tables

Table 8.1: Correlations between DF with λ_f, λ_d and ρ for corresponding LA locations.

LA locations	Correlation with λ_f	Correlation with λ_d	Correlation with ρ
LIPV	R^2<0.01, P=0.73	R^2<0.01, P=0.82	R^2<0.01, P=0.81
LSPV	R^2=0.02, P=0.43	R^2=0.01, P=0.52	R^2<0.01, P=0.66
RIPV	R^2<0.01, P=0.9	R^2<0.01, P=0.91	R^2<0.01, P=0.78
RSPV	R^2<0.01, P=0.77	R^2<0.01, P=0.78	R^2=0.02, P=0.44
LAA	R^2<0.01, P=0.77	R^2<0.01, P=0.8	R^2<0.01, P=0.63
LA anterior	R^2<0.01, P=0.74	R^2<0.01, P=0.7	R^2<0.01, P=0.65
LA septal	R^2=0.04, P=0.22	R^2=0.03, P=0.28	R^2=0.03, P=0.33
LA high posterior	R^2=0.02, P=0.48	R^2=0.01, P=0.52	R^2<0.01, P=0.9
LA low posterior	R^2<0.001, P=0.73	R^2<0.001, P=0.73	R^2<0.001, P=0.73
LA lateral	R^2<0.001, P=0.73	R^2<0.001, P=0.73	R^2<0.001, P=0.73

Data presented in R^2 and their associated P-values in all ten LA locations sampled.

8.8 Figures

Figure 8.1: Spatial distribution of DF in the LA

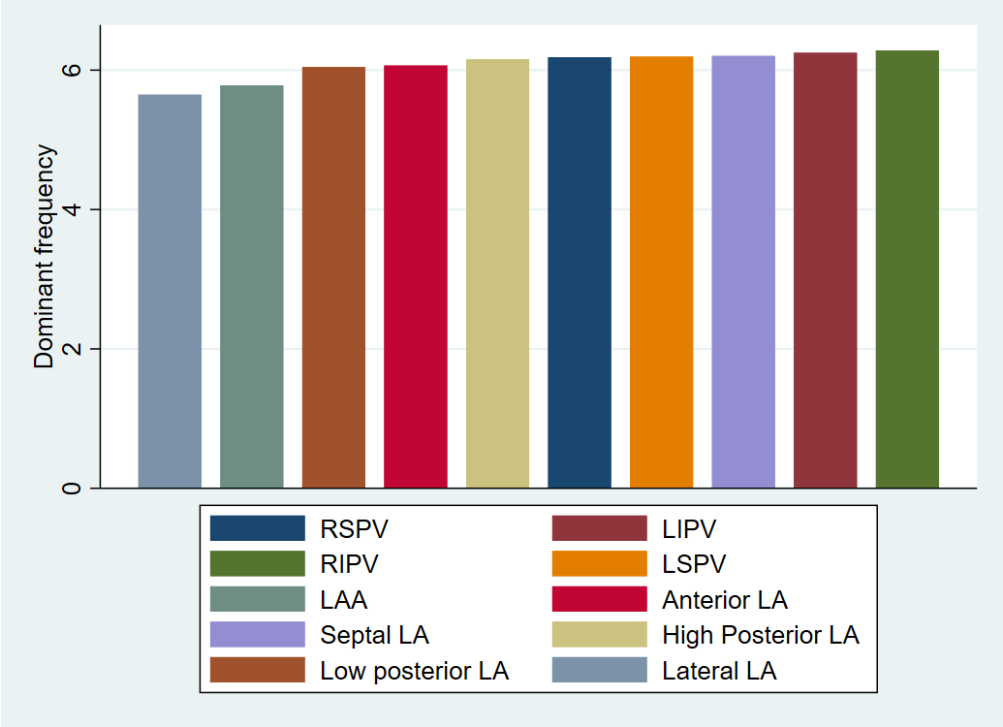


Figure 8.1: Figure 8.1 showing the spatial distribution of DF in all ten LA regions sampled, in all patients. Highest DF was observed in the RIPV followed by the LIPV while the lowest DF was observed in the lateral LA wall. In contrast, renewal rate constant was the highest in the LAA, while the lowest renewal rate constant was in the region of the LIPV and the low posterior LA wall. No significant correlations were observed in all ten LA regions sampled between DF and ρ (renewal rate constant) values.

Figure 8.2: Spatial distribution of DF in the LA, by AF Phenogroup

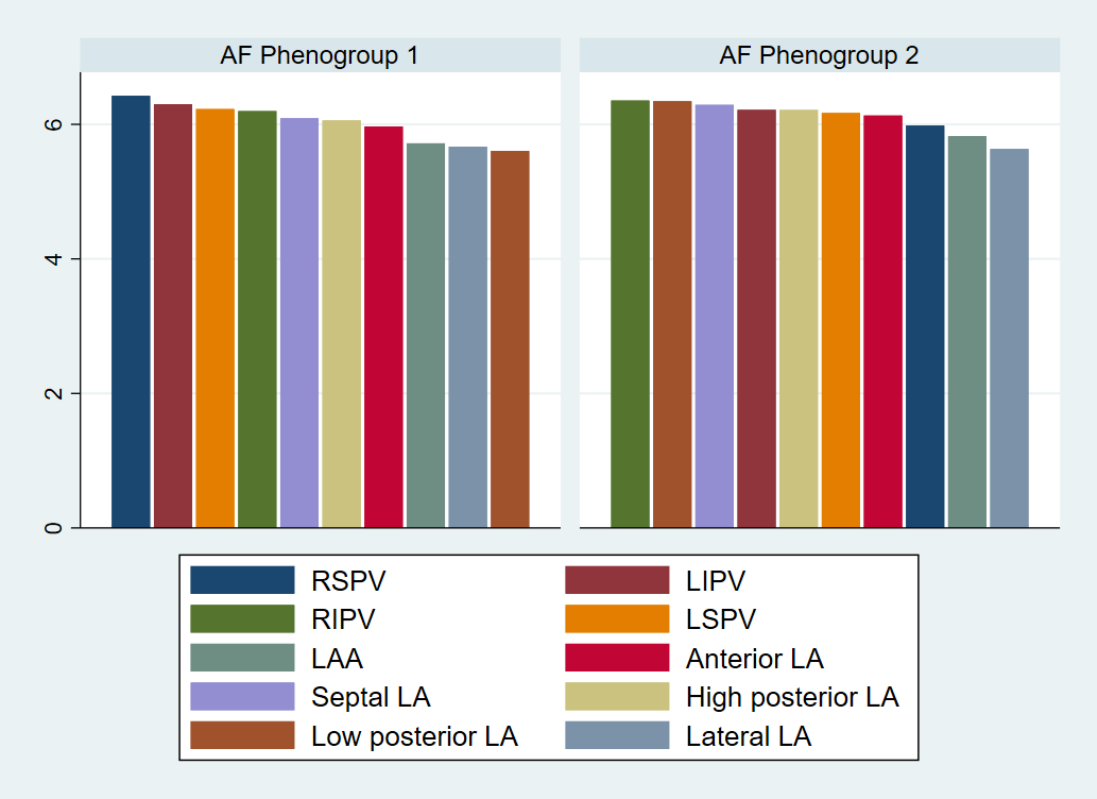
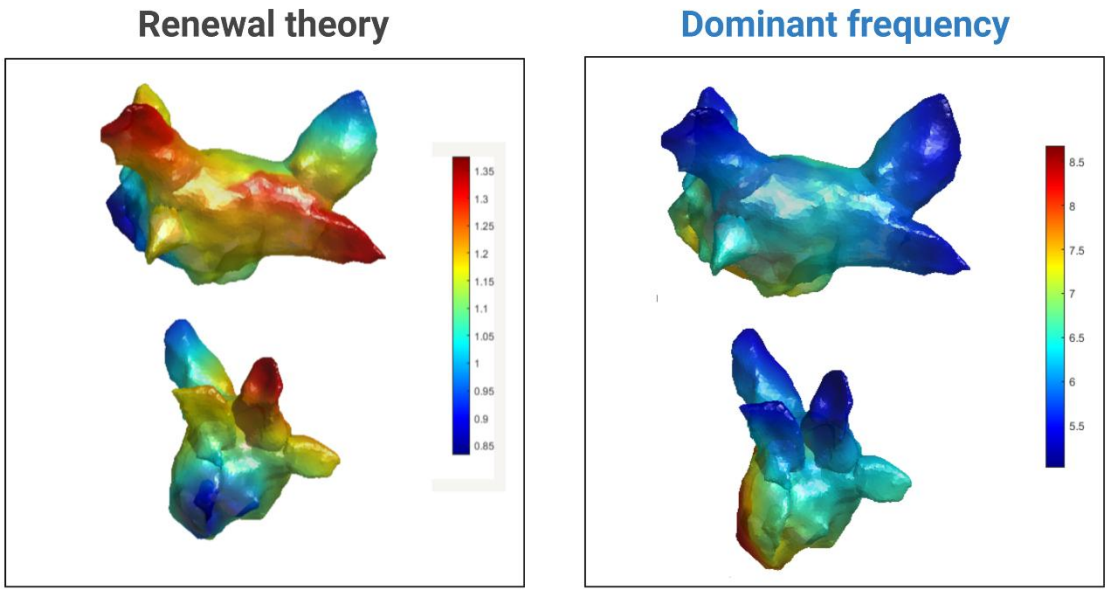


Figure 8.2: Figure 8.2 showing the spatial distribution of DF in all ten LA regions sampled, when analysed by AF Phenogroup. In AF Phenogroup 1, the highest DF region was observed in the RSPV, while in AF Phenogroup 2, the highest DF region was observed in the RIPV. In contrast, using the renewal theory, highest renewal rate constant region was in the LIPV in AF Phenogroup 1 patients and in the LAA in AF Phenogroup 2 patients (Chapter 4). No significant correlations were observed in all ten LA regions sampled between DF and ρ (renewal rate constant) values, when analysed by AF Phenogroup.

Figure 8.3: Spatial comparison between renewal theory-based analysis with dominant frequency analysis in patient 1.

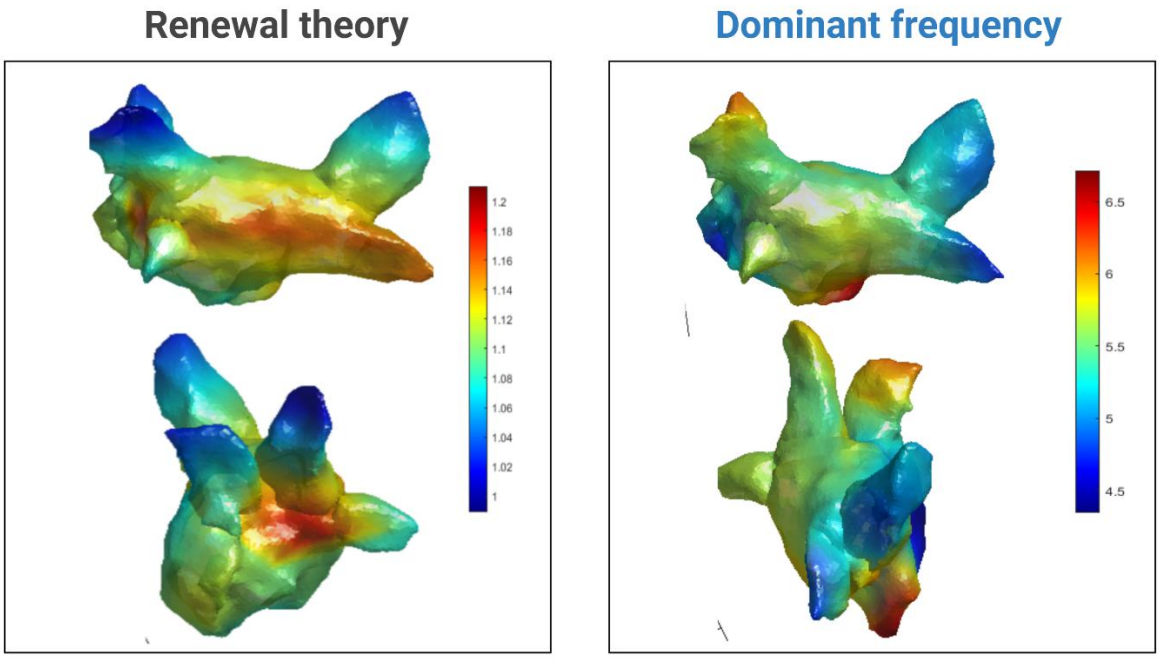


Top panel: PA view of the LA
Bottom panel: Left lateral view of the LA
Red region denotes region of the highest rho value
Highest rho region in LSPV, followed by RIPV

Top panel: PA view of the LA
Bottom panel: Left septal view of the LA
Red region denotes region of the highest DF value
Highest DF region in LA anterior wall

Red region denotes region with highest rho value, based on renewal theory (left panel) and highest dominant frequency value (right panel).

Figure 8.4: Spatial comparison between renewal theory-based analysis with dominant frequency analysis in patient 2.

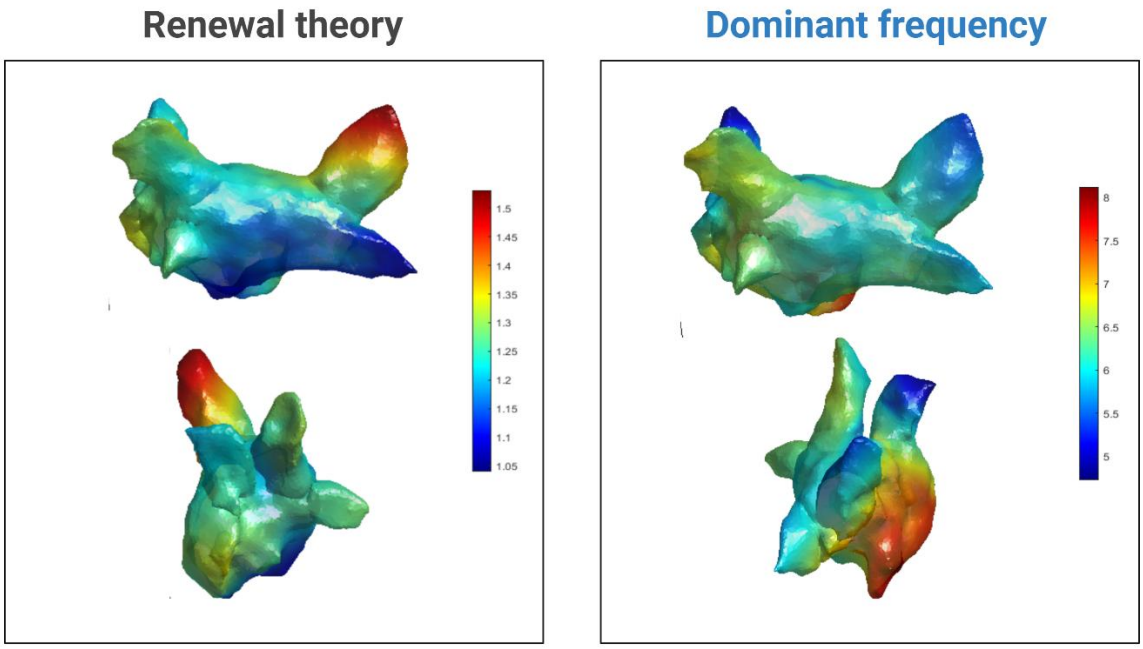


Top panel: PA view of the LA
Bottom panel: Left lateral view of the LA
Red region denotes region of the highest rho value
Highest rho region in LA lateral wall

Top panel: PA view of the LA
Bottom panel: Left septal view of the LA
Red region denotes region of the highest DF value
Highest DF region in LA septal wall

Red region denotes region with highest rho value, based on renewal theory (left panel) and highest dominant frequency value (right panel).

Figure 8.5: Spatial comparison between renewal theory-based analysis with dominant frequency analysis in patient 3.



Top panel: PA view of the LA
Bottom panel: Left lateral view of the LA
Red region denotes region of the highest rho value
Highest rho region in RSPV

Top panel: PA view of the LA
Bottom panel: Left septal view of the LA
Red region denotes region of the highest DF value
Highest DF region in LA septal wall

Red region denotes region with highest rho value, based on renewal theory (left panel) and highest dominant frequency value (right panel).

Chapter 9

Summary, future directions and concluding remarks

The presence of unstable re-entrant circuits, or rotors has long been observed in both paroxysmal and persistent forms of AF. However, their role in AF persistence remains poorly defined. Mechanistic understanding of AF persistence is crucial to help dictate effective ablation strategies in AF patients, particularly in those with persistent AF, a subgroup of patients who derive suboptimal benefits from AF ablation. An interesting behaviour of these rotors is that they are continuously formed and destroyed over time. Dharmaprani et al recently showed in animal models, optical mapping data and computer simulations that the lifetime and inter-arrival times for these rotors follow an exponential curve, consistent with the notion that rotors form and destroy by Poisson renewal processes. A systematic review performed showed similar exponential curves of the rotor lifetime and inter-formation times from six previously published studies. The motivation for this study is to extend the earlier validation findings of renewal theory in AF, as a new quantitative metric for fibrillatory dynamic analysis in AF to various electrical and structural markers of atrial remodelling linked to AF and further, assess its association with clinical outcomes of AF patients who underwent AF ablation.

9.1 Study 1 (Chapter 2) - Role of interatrial conduction in atrial fibrillation. Mechanistic insights from renewal theory-based fibrillatory dynamic analysis.

From a mechanistic perspective, an area of interest is the role of interatrial pathways during AF and the role of these pathways in AF persistence. However, studies in this field have been limited to date, given difficulties in analysing the chaotic nature of fibrillation.

In this study, we used different regions in the RA and LA, that are known to be connected by different interatrial pathways, namely the Bachmann's bundle, interatrial septum, and inferior interatrial routes, through the musculature of the coronary sinus. We observed the presence of electrical disrelation in the interatrial septum, measured by λ_f and λ_d, in patients with enlarged LA and persistent AF patients. Additionally, the highest statistical correlation was observed in the atrial regions connected by the inferior interatrial routes, followed by the interatrial septum. While the clinical significance of this is unclear at this stage, identifying atrial regions which have significant electrical disrelation may be of clinical importance to select a subset of AF patients who would potentially benefit from targeted ablation to these regions.

9.2 Study 2 (Chapter 3) - Spatial gradient of renewal rate constants at the pulmonary vein-left atrial junction: associations with the clinical outcomes of atrial fibrillation ablation.

In Chapter 2, we observed that spatial gradients of renewal rate constants enabled the evaluation of electrical connectivity between different interatrial regions during AF. Building on this and current knowledge of that PV-LA junction plays an important role in AF ablation, we hypothesised that the presence of spatial gradient between the PV and LA would predict clinical outcomes after a PVI-only procedure. In this study, we categorized AF patients into two main groups: AF Phenogroup 1, with a

positive PV-LA gradient and AF Phenogroup 2, with a negative PV-LA gradient. We observed a significantly higher AF burden, estimated using a non-invasive AliveCor monitor with earlier time to recurrence after ablation in AF Phenogroup 2. Interestingly, there was also no association seen between AF Phenogroup classification with currently used paroxysmal-persistent AF classification. It is plausible that electrophysiologic classification of AF using the renewal approach may better select AF patients who would benefit from a PVI-only approach, and further, also distinguished a subset of AF patients who were poorly responsive to a PVI-only strategy (AF Phenogroup 2).

9.3 Study 3 (Chapter 4) – Electrophysiological analysis of the left atrium using renewal theory.

In Chapter 3, we observed that electrophysiologically characterizing AF patients according to their AF Phenogroup, determined by the presence or absence of PV to LA renewal rate constant gradient was associated with improved clinical outcomes post-PVI-only procedure. Extending from these findings, we sought to electrophysiologically analyse the spatial distribution of renewal rate constants, depending on their AF Phenogroup classification. The rate of rotor formation and rate of rotor destruction, λ_f and λ_d were highly correlated in all atrial regions, suggesting a continuous process of rotor formation and destruction in AF. In AF Phenogroup 1, we observed higher renewal rate constants in all of the pulmonary veins, compared to AF Phenogroup 2 patients. In all patients and AF Phenogroup 2 patients, we observed highest renewal rate constants in the LAA.

9.4 Study 4 (Chapter 5) - Relationship between renewal-based electrophysiological analysis of the left atrium with echocardiographic markers of structural and functional remodelling.

Progressive LA structural and functional remodelling underlies AF progression and has previously been associated with poorer clinical outcomes after catheter ablation. In chapter 5, we aimed to investigate the association between AF Phenogroup, a new electrophysiological classification derived from renewal theory with echocardiographic markers of LA structural and functional remodelling. We hypothesised that AF Phenogroup 2 patients, a subset of AF patients with a loss of PV to LA gradient will have echocardiographic evidence of adverse atrial remodelling. Structurally, we observed a larger indexed LA volume in AF Phenogroup 2 patients. Functionally, there was a trend towards the significance of a lower LA ejection fraction in AF Phenogroup 2 patients, with no differences observed in other LA strain parameters, when compared with AF Phenogroup 1 patients. These findings suggest an association between AF Phenogroup 2 with adverse echocardiographic markers of LA structural and functional remodelling.

9.5 Study 5 (Chapter 6) - Role of the right atrium in atrial fibrillation. Electrophysiological insights from renewal theory-based fibrillatory dynamic analysis.

The role of RA in AF persistence remains poorly defined. In chapter 6, we explored the spatial distribution of renewal rate constants within the RA and their association with underlying RA structural and functional remodelling. In the analysis, we further classified AF patients according to the presence or absence of LA to RA renewal rate constant gradient. The reason for this distinction is that previous studies have shown potential clinical benefit in additional RA ablation in patients with loss of left to right AF cycle length or

dominant frequency gradient. We hypothesised that a negative LA to RA ρ gradient was a marker of adverse clinical outcomes in AF patients undergoing ablation and will be associated with adverse RA echocardiographic markers of structural and functional remodelling. In this study, we observed a significantly higher renewal rate constant in the right atrial appendage, which may be related to the complex musculature in the appendage, with the lowest ρ documented in the cavotricuspid isthmus region. AF patients with a loss of left to right ρ gradient showed evidence of adverse RA functional remodelling, with a higher burden of AF documented on AliverCor monitors after 6 months. After multivariate analysis, AF Phenogroup remained the only significant predictor of a loss of LA to RA ρ gradient.

9.6 Study 6 (Chapter 7) - Relationship between subclinical left ventricular systolic dysfunction and atrial structural, functional, and electrophysiological properties.

The presence of subclinical LV dysfunction has previously been associated with new-onset AF and adverse clinical outcomes after AF ablation. In this study, we aim to analyse the relationship between the presence of subclinical LV dysfunction with atrial electrophysiological changes, measured using renewal theory, and echocardiographic markers of atrial structural and functional remodelling. We divided the analysis into three sections.

In section 1, we analysed the spatial distribution of ρ in the LA and the presence of adverse echocardiographic markers of atrial structural and functional remodelling in AF patients with abnormal LV GLS. In AF patients with normal LV GLS, we observed that the ρ in the LA anterior wall was significantly higher when compared to AF patients with abnormal LV GLS. In addition, there was the presence of adverse biatrial structural and functional remodelling in AF patients with abnormal LV GLS.

In section 2, we analysed the effect of subclinical LV dysfunction in patients with normal LV ejection fraction on the spatial distribution of renewal rate constants in the LA and echocardiographic markers of biatrial structural and functional parameters. We did not observe any significant differences in the spatial distribution of ρ in the LA and RA comparing patients with abnormal versus normal LV GLS, in patients with documented normal LV ejection fraction. However, structural, and functional changes in the LA, along with functional changes in the RA were observed in AF patients with abnormal LV GLS, without any significant regional differences in renewal rate constants. It is plausible from our findings, functional and structural remodelling in the atrium occurs earlier before any significant electrophysiological changes in the atrium.

In section 3, we analysed the influence of abnormal LV GLS on electrophysiologic characteristics and clinical outcomes in AF Phenogroup 2 patients. We hypothesised that the presence of abnormal LV GLS in a subset of AF patients with AF Phenogroup 2 will be associated with unfavourable clinical outcomes after AF ablation. Not surprisingly, a significantly higher burden of biatrial structural and functional remodelling was observed in AF Phenogroup 2 patients with abnormal LV GLS. Clinically, there was a trend towards significance towards a higher AF burden, estimated using AliveCor monitor in AF Phenogroup 2 patients with abnormal LV GLS, when compared to AF Phenogroup 2 patients with abnormal LV GLS.

9.7 Study 7 (Chapter 8) - Relationship between renewal theory-based assessment of fibrillatory dynamics with dominant frequency analysis

Dominant frequency is a quantitative metric used to analyse fibrillatory dynamics in AF and was previously used clinically to identify “drivers” or substrates in AF, which may be targets for ablation. However, to date, clinical results from studies utilizing dominant frequency to guide ablation have so far been negative. In chapter 8, we analysed the mechanistic relationship between dominant frequency and renewal theory-based fibrillatory dynamic analysis. We observed no significant correlations between λ_f, λ_d and ρ with

dominant frequency in all ten LA locations. The highest dominant frequency value was in the inferior pulmonary veins while the highest ρ value was in the low posterior LA wall in all patients. When AF Phenogroup were considered, the highest ρ and dominant frequency value was observed in the inferior pulmonary veins in AF Phenogroup 1, while in AF Phenogroup 2, discrepancies in the highest ρ and dominant frequency atrial regions were observed. No significant relationship was observed between AF Phenogroup with a loss of PV to LA dominant frequency gradient.

9.8 Main limitations of findings from RENEWAL AF.

- Potential incorrect identification of PS stemming from limitations of multi-electrode mapping of phase singularities (440).
- Issue with incomplete data, with 75% of patients adhering to monitoring protocol via AliveCor Kardia mobile (84% in AF Phenogroup 2 and 86% in AF Phenogroup 1), with n=2 patients lost to follow up. However, the percentage of patients with remote rhythm monitoring for AF burden and percentage compliance of patients in RENEWAL-AF are comparable to that from another clinical study. For instance, in the randomised clinical study by Voskoboinik et al investigating the effect of alcohol abstinence of AF burden (414), only 82% of patients had remote monitoring either by AliveCor, pacemaker or implantable loop recorder combined. N=4 (2.8%) of patients who were non-adherent to the AliveCor monitor had 7-day Holter monitoring. Adherence to Kardia mobile recordings in this cohort was approximately 257 tracings (median) per patien during six months follow-up, with an interquartile range of 124 to 382. In the CAPLA trial, randomised study investigating the efficacy of pulmonary vein isolation plus posterior wall isolation in persistent AF patients, compliance rates to Kardia mobile transmissions were not reported in the manuscript. However, in patients deemed “non-compliant” to AliveCor transmissions, 24-hour Holter monitoring was used instead which was 16.7% in the pulmonary vein isolation group and

16.3% in the pulmonary vein isolation plus posterior wall isolation. This approximates the 85% compliance rate observed in this study.

- No post procedural blanking period was applied for follow up. However, there has been increasing number of studies suggesting that early recurrence of AF, specifically during the 3-months blanking period were predictive of late AF recurrence. Calkins et al performed a meta-analysis investigating the association between early AF recurrence (defined as before 3 months) and late AF recurrence (post blanking to 12 months or later), and included AF ablation studies using radiofrequency ablation, with repeated monitoring of arrythmia recurrence including asymptomatic recurrence (736). In nine studies involving n=2330 AF patients, the authors found that the absence of recurrence of AF during blanking period was highly predictive of the absence of late recurrence of AF, with a pooled negative predictive value of 89% in patients with paroxysmal AF and 91% in patients with persistent AF (736). Similarly, another meta-analysis involving n=3975 paroxysmal and persistent AF patients who underwent cryo-balloon pulmonary vein isolation procedures, the occurrence of early AF recurrence during blanking period was associated with a higher risk of late AF recurrence in both paroxysmal and persistent AF patient, with an odds ratio (OR) of 5.31, 95% confidence interval (CI) 3.75-7.51, and this risk was equally high in patients with paroxysmal AF, OR 7.16, 95% CI 4.4-11.65 and persistent AF, OR 7.63, 95% CI 3.62-16.07 14 (737).
- The sample size was small (n=41 patients) with a short duration of follow up, of six months.

9.9 Future directions

- Findings from RENEWAL-AF need to be confirmed in a larger prospective study, using higher density electroanatomic maps and sampling from a larger number and area of locations within the atrial chamber to improve sampling coverage.
- A mechanistic reason that has been proposed for AF persistence is the presence of endo-epicardial dissociation in AF. It is possible to explore this hypothesis using the renewal approach. This can be achieved by simultaneous recordings of AF electrograms on the endocardium and epicardium in AF patients, and subsequently, measuring the correlations between the renewal rate constants on both atrial surfaces.
- Electrophysiologic characterisation using AF Phenogroup relies on the invasive assessment of λ_f/λ_d, limiting the use of this new AF classification to clinical practice. Further studies are required to investigate the accuracy of assessment of λ_f/λ_d using surface ECG and electrograms on implantable cardiac devices. Another exciting prospect would be the use of a high-density multi-electrode ECG vest to assess λ_f/λ_d, which could be important to assess the spatiotemporal distribution of λ_f/λ_d.
- While there are increasing body of evidence linking improved clinical outcomes with AF ablation procedures, an initial invasive approach for AF is logistically not possible in many cardiac centres globally. Future studies looking at the timing of AF ablation guided by changes in λ_f/λ_d could potentially be useful to sub-select a group of AF patients who would benefit from earlier AF ablation procedures.
- Antiarrhythmic drug therapy for AF patients has been associated with a high failure rate, with significant side effects. An interesting mechanistic study would be to investigate the effects of different antiarrhythmic therapies on renewal rate constants and changes in both λ_f and λ_d that

predict termination. From a mechanistic standpoint, this will improve our understanding of changes in fibrillatory dynamics during AF termination. Clinically, renewal rate constants could also potentially be used to monitor antiarrhythmic drug response in AF patients.

- Real-time modulation of λ_f/λ_d could assist in dictating appropriate ablation strategies for AF patients undergoing ablation, particularly in patients with persistent AF, where strategies beyond PVI are still in question. Similarly, in patients undergoing re-do AF ablation procedures, computational modelling, and simulation of changes of λ_f/λ_d based on different ablation strategies could be performed before the planned re-do AF ablation procedure.

- The findings of RENEWAL-AF may also have implications for the development of new approaches to the clinical classification of AF based on the physiological dynamics of the fibrillatory process. The favourable clinical outcomes associated with PVI in Phenogroup 1 over Phenogroup 2 are consistent with a notion that the fibrillatory process may evolve from a pulmonary vein-based phenomenon towards to a more spatially generalised dynamics affecting the body of the atria. Concordant with this notion is that contemporary risk factors for AF progression, such as CHA_2DS_2-VaSC score, and LA size markers were correlated with Phenogroup 2 classification. On the other hand, time spent in AF as determined by AF pattern classification only partially overlapped with the Phenogroup classification. It is possible that the AF Phenogroup classification developed here in the context of AF ablation patients, could have implications for understanding the mechanistic progression of AF in non-ablation cohorts.

- Finally, defining PVI-responders using λ_f/λ_d could help delineate a subset of patients who would require further additional ablation, beyond PVI-only ablation.

9.9 Concluding remarks

Observations from a previous study by Dharmaprani et al validated the use of renewal theory, as a novel quantitative metric for fibrillatory dynamic analysis in animal, computational and human models of AF. Findings from the studies discussed in this dissertation demonstrated links between renewal theory with underlying cardiac biological changes that occur in AF. Importantly, electrophysiologic classification of AF patients according to AF Phenogroup, allowed distinction of a subset of AF patients who may respond favourably to PVI-only procedure. This observation is of significant clinical importance, as it could improve patient selection for additional substrate modification for AF. Collectively, these studies have improved our mechanistic understanding regarding AF-related electrophysiological changes and demonstrated the potential clinical utility of renewal theory-based fibrillatory dynamic analysis in AF, which could potentially be used to guide future AF therapies.

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